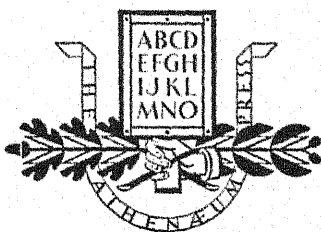


# THE Carbon Compounds

A TEXTBOOK  
OF ORGANIC CHEMISTRY BY  
C. W. PORTER  
PROFESSOR OF CHEMISTRY  
IN THE UNIVERSITY OF CALIFORNIA

*THIRD REVISED EDITION*



GINN AND COMPANY

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## PREFACE

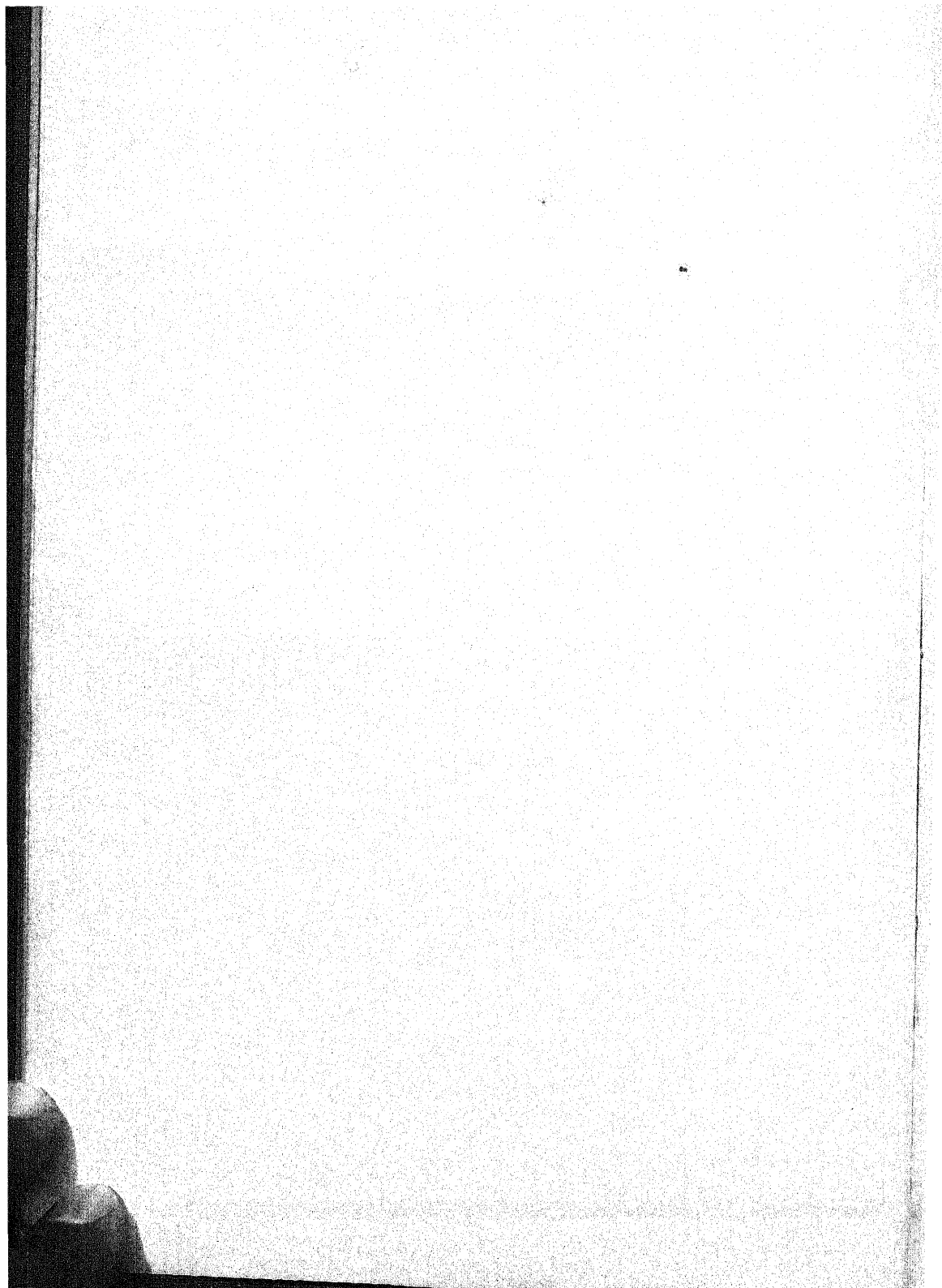
This book constitutes an outline of an elementary course in organic chemistry. Its scope is limited to fundamental principles and general reactions. The publishers have permitted frequent revisions and this policy has made it possible to keep the book in step with recent advances in the field of chemistry.

The first main division is devoted, almost exclusively, to the aliphatic series of compounds; the second division deals with the aromatic series; and the third part is a review of the more important general organic reactions.

An apology should be offered for including a description of benzene in the section devoted to aliphatic hydrocarbons. An early acquaintance with cyclic structures is desirable, for benzene is used as a solvent from the beginning in the laboratory work and at least two of its derivatives, benzenesulfonyl chloride and phenylhydrazine, are mentioned as useful reagents very early in the theoretical part of the course. It is not considered necessary to change the main classifications on account of brief discussions of cyclic compounds which have been incorporated in the first chapter of the book.

There are many references to current literature and to discussions presented in the following books: Meyer and Jacobson, *Lehrbuch der organischen Chemie*; Richter, *Chemie der Kohlenstoffverbindungen*; Beilstein, *Handbuch der organischen Chemie*; Sidgwick, *Organic Chemistry of Nitrogen*; Cohen, *Organic Chemistry*; Weyl, *Die Methoden der organischen Chemie*; Pictet, *The Vegetable Alkaloids*; and Mulliken, *Identification of Pure Organic Compounds*. The list is given here not only as an acknowledgment of indebtedness to the authors but also for the purpose of directing the attention of the student to a very valuable group of reference books.

C. W. PORTER



# CONTENTS

|   | PAGE |
|---|------|
| INTRODUCTION . . . . .  | 1    |
| Analytical methods. Classification. Homology. Isomerism. Valence.   |      |
| ALIPHATIC COMPOUNDS   |      |
| HYDROCARBONS . . . . .  | 9    |
| The methane series. Properties. Alkyl radicals. Methods for preparing the saturated hydrocarbons. Structure and isomerism. Nomenclature. The ethylene series. Isomerism and nomenclature of the olefins. Reactions of the ethylene series. Geometrical isomerism. The allylene series. The acetylene series. Preparation, properties, and nomenclature of acetylene hydrocarbons. The alicyclic series. The benzene series. Thermochemical relations. |      |
| ALCOHOLS . . . . .  | 39   |
| Saturated monohydric alcohols. Physical properties. Classification. Chemical properties. Nomenclature. Isomerism. Polyhydric alcohols. Unsaturated alcohols. Mercaptans.  |      |
| ALKYL HALIDES AND PARAFFIN POLYHALIDES . . . . .  | 52   |
| ETHERS . . . . .  | 62   |
| ALDEHYDES AND KETONES . . . . .   | 66   |
| Nomenclature. Preparation. Addition reactions. Reduction. Oxidation. Other reactions.   |      |
| MONOBASIC ACIDS AND THEIR DERIVATIVES . . . . .   | 81   |
| Saturated acids. Preparation. Acyl radicals. Unsaturated acids. Acid chlorides. Acid anhydrides. Esters of organic acids. Esters of inorganic acids. Acid amides. Halogen derivatives. Amino acids. Hydroxy acids.  |      |
| OPTICAL ISOMERISM . . . . .   | 113  |
| POLYBASIC ACIDS AND THEIR DERIVATIVES . . . . .   | 121  |
| Esters of dibasic acids. Acid anhydrides. Amides of dibasic acids. Unsaturated acids. Hydroxy acids.  |      |
| ALIPHATIC AMINES . . . . .  | 136  |
| Preparation. Properties. Dissociation constants. Ammonia system.  |      |
| CYANIDES AND CYANATES . . . . .   | 145  |
| Cyanides and isocyanides. Cyanates, isocyanates, and fulminates.  |      |

|  | PAGE |
|--|------|
| THE CARBOHYDRATES . . . . .  | 151  |
| Mutarotation. Gamma-sugars. Methylglucosides. Reactions of the monosaccharides. Configurations of the monosaccharides. The disaccharides. Polysaccharides. |      |
| ENZYMES . . . . .  | 182  |
| AROMATIC COMPOUNDS   |      |
| HYDROCARBONS . . . . .   | 185  |
| Constitution of benzene. Homologues of benzene. Condensed nuclei.  |      |
| HYDROCARBON DERIVATIVES . . . . .  | 204  |
| Aryl halides. Sulfonic acids. Nitro compounds. Derivatives of nitrobenzene. Reduction of nitrobenzene.   |      |
| AROMATIC AMINES . . . . .  | 216  |
| Primary amines. Homologues of aniline. Naphthylamines. Secondary amines. Tertiary amines. The diazo reaction. Hydrazines.                                  |      |
| PHENOLS . . . . .  | 231  |
| Monohydric phenols. Cresols. Naphthols. Dihydric phenols. Trihydric phenols.   |      |
| ALCOHOLS, ALDEHYDES, AND KETONES . . . . .   | 242  |
| Alcohols. Aldehydes. Ketones.  |      |
| AROMATIC ACIDS AND THEIR DERIVATIVES . . . . .   | 247  |
| Monocarboxylic acids. Dicarboxylic acids.  |      |
| ORIENTATION AND STERIC INFLUENCES OF SUBSTITUENTS . . . . .  | 254  |
| Directing influences of substituents. Enhanced activity. Diminished activity.  |      |
| FREE RADICALS . . . . .  | 266  |
| DYES . . . . .   | 271  |
| Azo dyes. Triphenylmethane dyes. The phthaleins. Alizarin dyes. Indigoid dyes. Structure and color.  |      |
| THE PROTEINS . . . . .   | 291  |
| Amino acids. Structure of the proteins. Synthesis of polypeptides. Hydrolysis of proteins. Classification. Qualitative reactions. Protein salts.           |      |
| VITAMINS . . . . .   | 311  |
| PURINES AND PYRIMIDINES . . . . .  | 316  |
| THE ALKALOIDS . . . . .  | 326  |
| Coniine. Nicotine. Atropine. Cocaine. Strychnine. Morphine. Cinchonine and quinine. Piperine.  |      |

|   | PAGE |
|---|------|
| ESSENTIAL OILS . . . . .  | 349  |
| Terpenes. Olefinic terpenes and their derivatives. Monocyclic terpenes.<br>Dicyclic terpenes. Flavors and perfumes not related to terpenes.   |      |
| GENERAL ORGANIC REACTIONS   |      |
| HYDROLYSIS . . . . .  | 365  |
| OXIDATION . . . . .   | 370  |
| REDUCTION . . . . .   | 379  |
| CONJUGATION AND RESONANCE . . . . .   | 385  |
| CONDENSATION PROCESSES . . . . .  | 395  |
| The Grignard reaction. Zinc alkyl reactions. The Friedel and Crafts<br>reaction. Electrolysis of salts. The Wurtz synthesis. The aldol con-<br>densation. The benzoin condensation. The Cannizzaro reaction. The<br>Perkin reaction. Gabriel's synthesis. Acetoacetic ester. Malonic ester. |      |
| STRUCTURAL REARRANGEMENTS . . . . .   | 431  |
| The Hofmann rearrangement of amides. The Lossen rearrangement. The<br>Stieglitz rearrangement. The Curtius rearrangement. The Beckmann re-<br>arrangement. The pinacol rearrangement. The benzil rearrangement.<br>The Hofmann rearrangement of amines. The Walden inversion.               |      |
| APPENDIX . . . . .  | 459  |
| Formulas. Molecular weights from properties of gases. Molecular weights<br>from properties of solutions. Vapor pressure. Boiling point and freezing<br>point. Osmotic pressure.   |      |
| QUESTIONS AND PROBLEMS . . . . .  | 469  |
| INDEX . . . . .   | 485  |

## ABBREVIATIONS

The abbreviations adopted by the American Chemical Society are used in this book. For complete list see *Chemical Abstracts*, Vol. 25, No. 22 (November 20, 1931). Titles of journals are abbreviated as follows:

- Am. Chem. J.* The American Chemical Journal.
- Am. J. Med. Sci.* The American Journal of Medical Sciences.
- Am. J. Sci.* The American Journal of Science.
- Ann.* Annalen der Chemie (Liebig's).
- Ann. chim. et phys.* Annales de chimie et de physique.
- Ber.* Berichte der deutschen chemischen Gesellschaft.
- Biochem. J.* The Biochemical Journal.
- Bull. soc. chim.* Bulletin de la société chimique de France.
- Chem. Rev.* Chemical Reviews.
- Chem. Zeit.* Chemiker Zeitung.
- Chem. Zentr.* Chemisches Zentralblatt.
- Compt. rend.* Comptes rendus de l'Académie des sciences.
- Gazz. chim. ital.* Gazzetta chimica italiana.
- J. Am. Chem. Soc.* The Journal of the American Chemical Society.
- J. Am. Med. Assoc.* The Journal of the American Medical Association.
- J. Biol. Chem.* The Journal of Biological Chemistry.
- J. Chem. Educ.* The Journal of Chemical Education.
- J. Chem. Phys.* The Journal of Chemical Physics.
- J. Chem. Soc.* The Journal of the Chemical Society (London).
- J. Ind. Eng. Chem.* The Journal of Industrial and Engineering Chemistry.
- J. Phys. Chem.* The Journal of Physical Chemistry.
- J. prakt. Chem.* Journal für praktische Chemie.
- Monatsh.* Monatshefte für Chemie.
- Phil. Mag.* The Philosophical Magazine and Journal of Science (London).
- Phys. Rev.* Physical Reviews.
- Proc. Chem. Soc.* Proceedings of the Chemical Society (London).
- Proc. Nat. Acad. Sci.* Proceedings of the National Academy of Sciences of the United States of America.
- Proc. Roy. Soc.* Proceedings of the Royal Society of London.
- Rec. trav. chim. Pays-Bas.* Recueil des travaux chimiques des Pays-Bas.
- Rev. gén. sci.* Revue générale des sciences pures et appliquées.
- Trans. Chem. Soc.* Transactions of the Chemical Society (London).
- Trans. Roy. Soc. Canada.* Transactions of the Royal Society of Canada.
- Z. physik. Chem.* Zeitschrift für physikalische Chemie.

# THE CARBON COMPOUNDS

## INTRODUCTION

The use of the terms *organic* and *inorganic* as applied to chemistry developed as a result of attempts to classify chemical substances on the basis of origin. All compounds formed in the tissues of living organisms — plants and animals — were called organic. Those found in the mineral kingdom were called inorganic compounds. The earlier chemists believed that it would never be possible to synthesize organic compounds except through the agency of life. It is still customary to attribute to vital forces many phenomena that cannot be reproduced by artificial means; but the element of mystery is disappearing, and every year experimental methods are developed to make new inroads upon the domain of vital forces. Already hundreds of compounds that are typical products of living cells have been synthesized from inorganic sources in the apparatus of the laboratory. They have been built up through applications of the general laws of physics and chemistry, without the intervention of mysterious forces. The majority of these compounds contain carbon, and, owing to certain peculiarities of carbon recognized only within the last century, the study of these compounds seemed hopeless to the earlier investigators. We now define organic chemistry as the chemistry of carbon compounds.

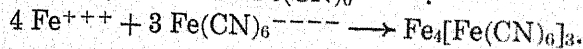
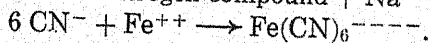
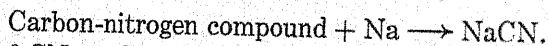
Approximately 300,000 compounds of carbon are known. The vast majority of these contain carbon with one or more of the following elements: hydrogen, oxygen, nitrogen, sulfur, chlorine, bromine, iodine, phosphorus.

**Analytical methods.** The practical methods used to purify and identify these substances, as well as the methods of analysis, are explained in detail in the laboratory manual.\* The principles underlying the analytical procedures are very simple.

\* Porter, Stewart, and Branch, *The Methods of Organic Chemistry*. Ginn and Company.

but it requires very great skill in the manipulation of apparatus to secure accurate results.

Carbon and hydrogen are determined by oxidizing the sample with hot copper oxide. The hydrogen contained in the sample is converted quantitatively into water, which is absorbed by calcium chloride or sulfuric acid, and weighed. The carbon of the sample is simultaneously converted into carbon dioxide, which is absorbed by potassium hydroxide solution, and weighed. When an organic nitrogen compound is decomposed by hot copper oxide, and the resulting gases are passed over hot metallic copper, nitrogen escapes in the free state. The gas is collected, freed from carbon dioxide by means of sodium hydroxide, and finally measured in a gas burette over water or mercury. A qualitative test for nitrogen is made by heating the compound with sodium and testing the product for cyanide ion. An aqueous extract of the fused mass is treated with ferrous and ferric sulfates, then acidified. A blue precipitate of ferrous-ferric cyanide reveals the presence of nitrogen. The reactions may be represented as follows:



A substance to be analyzed for sulfur is oxidized by concentrated nitric acid at 300° C. in a sealed tube. The sulfur is converted into sulfuric acid. Barium chloride is added, and the sulfur is estimated from the weight of barium sulfate precipitated. In the same way phosphorus is converted into phosphoric acid, then estimated by the usual inorganic procedure. Halogen compounds are heated in sealed tubes with fuming nitric acid and solid silver nitrate. The silver halide formed is washed and weighed. A combustion method for analyzing halogen compounds has been developed by Reid. The halogen is absorbed by a mixture of powdered silver and silver oxide.\*

**Classification.** Organic compounds are classified as *aliphatic* or *aromatic*. The division referred to as aliphatic comprises the compounds in which the carbon atoms are linked together in open chains or rows. The name was originally applied to the fats (*ἄλειφαρ*, "fat"). The fats now constitute only a minor group

\* Reid, *J. Am. Chem. Soc.*, 34, 1033 (1912).

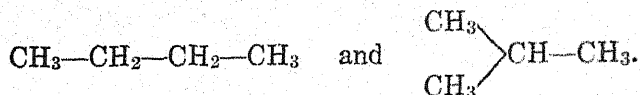


in the aliphatic division. The term *aromatic* was originally applied to compounds characterized by agreeable aromas. Almond oil, cinnamon, and vanilla were among the natural products originally classified as aromatic. Most of the compounds that were grouped together on the basis of odor are derivatives of benzene, and now, without reference to odor, all derivatives of benzene are said to belong to the aromatic series. In benzene and in each of its homologues there is a closed chain or ring of carbon atoms. The members of the aromatic series, therefore, are often referred to as cyclic compounds.

**Homology.** The study of organic chemistry is simplified by the fact that its thousands of compounds fall into a comparatively few groups or classes. The individual members in a class have certain properties in common. In many cases the compounds constituting a class are so related that, when arranged in the order of their molecular weights, there is a constant difference in composition between successive members. Such a group of compounds constitutes a homologous series. We have, for example, the hydrocarbons methane,  $\text{CH}_4$ ; ethane,  $\text{C}_2\text{H}_6$ ; and propane,  $\text{C}_3\text{H}_8$ . The difference in composition between successive members is  $\text{CH}_2$ . Corresponding to this difference in composition and molecular weight, there is a gradual change in properties such as density, solubility, and capacity to act with certain reagents. From the characteristics of a few of the lower, intermediate, and higher members of a homologous series we learn the trend in physical and chemical properties as applied to the group. We can then predict, with fair precision, the properties of any individual compound in the series.

**Isomerism.** Compounds having the same elementary composition and the same molecular weight, yet differing in chemical and physical properties, are known as *isomers*. Since isomers have the same empirical formula, the differences in properties must be due to different orientations of the atoms within the molecules. Ethyl alcohol and methyl ether have the formula  $\text{C}_2\text{H}_6\text{O}$ . The arrangements of the atoms in the two molecules are represented by the structural formulas  $\text{CH}_3\text{—CH}_2\text{OH}$  and  $\text{CH}_3\text{—O—CH}_3$ . In the alcohol the two carbon atoms are held together by a direct valence bond. In the ether an oxygen atom intervenes between the carbon atoms. In the alcohol there is a hydroxyl group. In the ether there is no hydrogen atom attached to oxygen. These structural details account for the

chemical and physical properties of the two compounds. Two hydrocarbons having the same empirical formula,  $C_4H_{10}$ , are represented by the following graphic or structural formulas:



There are other types of structural differences that give rise to isomerism. Asymmetric molecules, as much alike as an object is like its own mirror image, are not identical in properties. Such pairs of compounds have similar groups attached to corresponding atoms in the molecules, but the positions of these groups in space are not identical. The molecules constituting the pair are different in the same sense that the right and left hands are different. These are known as space isomers or stereoisomers. Changes in the positions of atoms or groups with respect to a double bond or a triple bond may give rise to isomers. Any variation in the arrangement of the atoms in a molecule imparts new properties to the compound. Many examples will be considered in detail later.

**Valence.** As early as 1804 John Dalton reached the conclusion that molecules of compounds are formed through the union of indivisible units which he called atoms. On the basis of this assumption it was possible to account for the law of definite proportions and the law of multiple proportions. Fifty years later Frankland\* observed that each atom has a saturation capacity, now called valence, which can be measured in terms of the number of atoms of other elements with which it will combine. He was able to formulate a useful rule of valence which could be applied in most cases as an aid in writing the formulas of new compounds. Hydrogen was adopted as the reference element with a valence of 1, for an atom of hydrogen was not known to combine with more than one atom of any element. Since one atom of oxygen combines with two of hydrogen, the valence of oxygen was said to be 2. The physical interpretation of valence, in Frankland's time, involved the assumption of a definite number of points on the surface of each atom admitting of mechanical attachment to corresponding points on other atoms. From the formulas  $CH_4$ ,  $CO_2$ , and  $CCl_4$ , carbon was assigned a valence of 4. The maximum

\* Frankland, *Phil. Trans.*, 142, 417 (1852).

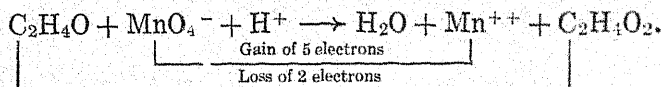
capacity of an atom to combine with other atoms is not always reached in compound formation. In carbon monoxide, for example, the valence of carbon is 2. The valence of an atom is a measure of the number of chemical bonds that tie it to other atoms. This is the original meaning of valence and it is still a satisfactory definition of the term.

It has become customary in inorganic chemistry to assign a positive or a negative sign to the number representing the valence of an atom or of a radical. In the compound  $\text{BaCl}_2$  the barium atom is said to have a valence of  $+2$  and each chlorine atom a valence of  $-1$ . The sign of the charge is determined by the direction of migration of the corresponding ion when conducting a current of electricity, and its numerical value is determined by the quantity of electricity that it transports. The number of charges carried by an ion is numerically equal to the valence of the atom or radical constituting the ion, but we should make a distinction between the valence of barium, which is 2, and the charge carried by the barium ion, which is  $+2$ . The latter is appropriately called the polar number of barium. The charge on the sulfate ion,  $\text{SO}_4^{--}$ , is  $-2$  and the same is true of the sulfite ion,  $\text{SO}_3^{--}$ . The valence of either of these radicals is 2 and the polar number of each ion is  $-2$ . When we speak of the valence of sulfur in the sulfate ion as  $+6$ , and in the sulfite ion as  $+4$ , we are using the term *valence* to designate various states of oxidation. It is obvious that an old term is being overworked in an attempt to make it cover several phenomena.

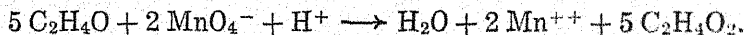
In this course we shall use the term *valence* in its original sense, and we shall employ the term *polar number* for the charge on an ion and for the hypothetical charge on an atom in an undissociated molecule. The valence of carbon in  $\text{CH}_2\text{Cl}_2$  is 4. We may think of the polar number of carbon in this compound as 0; but since this compound does not ionize, the polar number assigned to the carbon atom is fictitious.

In balancing oxidation and reduction equations, however, it is often advantageous to assign polar numbers to represent the various states of oxidation in which carbon atoms exist. Acetaldehyde,  $\text{C}_2\text{H}_4\text{O}$ , is oxidized to acetic acid,  $\text{C}_2\text{H}_4\text{O}_2$ , by an acid solution of a permanganate. Assigning to each hydrogen atom a polar number of  $+1$  and to each oxygen atom  $-2$ , we find it necessary to assign a charge of  $-2$  to the two carbon

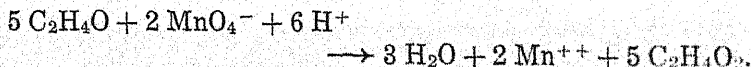
atoms in acetaldehyde in order to represent the molecule as electrically neutral. Similarly, we must assign a zero charge to the two carbon atoms in acetic acid in order to represent this molecule as an electrically neutral substance. We may think of the oxidation and reduction as the withdrawal of two electrons from the carbon atoms in each acetaldehyde molecule and the acquisition of five electrons by each manganese atom. The polar number of manganese changes from +7 in  $\text{MnO}_4^-$  to +2 in  $\text{Mn}^{++}$ . The hypothetical polar number of carbon changes from -1 in acetaldehyde to 0 in acetic acid. The equation for the reaction is balanced as follows:



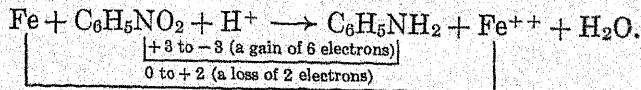
We must use two moles of permanganate ion and five of acetaldehyde to provide for the exchange of electrons between carbon and manganese.



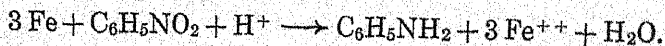
To balance the electrical charges (and also the atoms of oxygen and hydrogen), the complete equation becomes



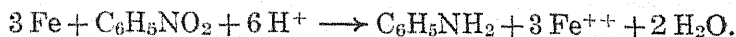
Nitrobenzene,  $\text{C}_6\text{H}_5\text{NO}_2$ , is reduced to aniline,  $\text{C}_6\text{H}_5\text{NH}_2$ , by treatment with iron and hydrochloric acid. The group  $\text{C}_6\text{H}_5$  remains unchanged. In order to estimate the charge on the nitrogen atom we may assign to the group  $\text{C}_6\text{H}_5$  a polar number of +1 in each of the compounds containing this group, or we may neglect the group entirely, since it appears in the same form on both sides of the equation. Using the value of +1 for the  $\text{C}_6\text{H}_5$  group, -2 for oxygen, and 0 for metallic iron, we may represent the electronic changes as follows:



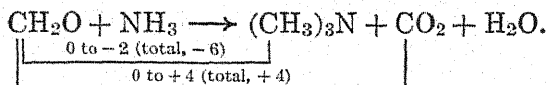
We must use six atoms of iron to reduce two molecules of nitrobenzene or three atoms of iron to reduce one of nitrobenzene:



To balance the electrical charges we must use six hydrogen ions. The completed equation becomes



If some molecules of a reagent are oxidized and other molecules of the same compound are reduced, the equation may be balanced in the same way. Let us consider a reaction between formaldehyde and ammonia. When the mixture is heated in an autoclave, the products formed are trimethylamine,  $(\text{CH}_3)_3\text{N}$ , water, and carbon dioxide:



The reduction of formaldehyde to trimethylamine involves a gain of two electrons for each carbon atom; and since there are three carbon atoms in the product formed, six electrons must be provided. The oxidation of formaldehyde to carbon dioxide involves a loss of four electrons. Therefore trimethylamine and carbon dioxide molecules must be produced in the ratio of 4 to 6, or 2 to 3. Expressing this ratio in the smallest possible whole numbers, we have



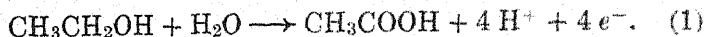
To obtain nine carbon atoms and two nitrogen atoms, as now indicated, in the products of the reaction, we must use nine molecules of formaldehyde and two of ammonia:



Oxidation and reduction equations may be balanced without reference to polar numbers by a device known as the method of *half reactions*. This system is familiar to all who are accustomed to writing equations for reactions occurring at the electrodes in electric cells. As an illustration let us consider the oxidation of alcohol to acetic acid by an acidic solution of potassium dichromate. One half of the reaction is the oxidation of alcohol molecules. The other half of the reaction is the reduction of dichromate ions. We shall balance these half reactions separately.

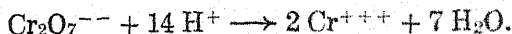
Using water as the source of the necessary oxygen, and assuming that in the oxidation process alcohol and water are con-

verted into acetic acid and hydrogen ions, the reaction is

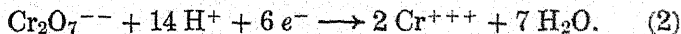


To balance the positive charges on the hydrogen ions we include in the equation four electrons,  $e^-$  (four negative charges).

Fourteen hydrogen ions are required to accomplish the conversion of  $\text{Cr}_2\text{O}_7^{--}$  into  $\text{Cr}^{+++}$  and  $\text{H}_2\text{O}$ .



So far as the elements are concerned this equation is balanced in its present form, but the electrical charges are not balanced. We have an excess of twelve positive charges on the left side and only six positive charges on the right side of the arrow. We must adjust this difference by adding six electrons to the left-hand side of the equation, which becomes

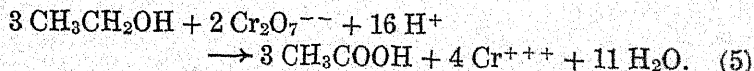


The equation in this form indicates that the oxidizing capacity of the dichromate ion is six equivalents per mole.

Before these half reactions (1) and (2) can be combined we must have as many electrons supplied by one reaction as are used by the other. We are using  $6 e^-$  in equation (2) and producing  $4 e^-$  in equation (1). Multiplying equation (1) by 3 and equation (2) by 2, we have  $12 e^-$  in each half reaction, and these cancel out when the two half reactions are added.



Adding equations (3) and (4) and canceling electrons, ions, and molecules so far as they occur on both sides of the arrow, we obtain a balanced equation (5) for the complete reaction.



Although this equation was derived from a consideration of hypothetical half reactions, it accurately represents the result of adding alcohol to an acidic solution of a dichromate. The chief merit of the *half reaction* system is that it requires no assumption concerning the distribution of charges in the reacting ions and molecules. It is based upon the number of electrons lost or gained and not upon the orientation of these electrons.

# ALIPHATIC COMPOUNDS

## HYDROCARBONS

### THE METHANE SERIES

Compounds composed of hydrogen and carbon only are known as hydrocarbons. Acetylene, ethylene, ethane, and benzene are well-known compounds of this type. We shall consider first the saturated hydrocarbons of the aliphatic series.

A compound is said to be saturated if it fails to form an addition product when treated with a halogen or with a halogen acid. It is unsaturated if it forms an addition product with such a reagent. Ethylene, for example, reacts with chlorine, forming a compound which contains chlorine in addition to all the carbon and hydrogen of the original ethylene molecule. This is a typical *addition reaction*, and ethylene is classified as an unsaturated hydrocarbon. On the other hand, when ethane reacts with chlorine, hydrogen atoms are removed from the ethane molecule and a chlorine atom takes the place of each hydrogen atom so removed. Such a process is called a *substitution reaction*. Ethane is said to be a saturated hydrocarbon. Unsaturated as well as saturated compounds may, under suitable conditions, form substitution products, but only unsaturated compounds form stable addition products.

Methane,  $\text{CH}_4$ , commonly called marsh gas, is the first member of the saturated series of hydrocarbons, and the entire group is known as the methane series. The group is referred to also as the paraffin series or the saturated series.

The first four members of the series are arbitrarily named methane, ethane, propane, and butane. The name of each higher member is derived from the Greek numeral corresponding to the number of carbon atoms in the molecule. It will be observed that the members of the series differ from each other in composition and molecular weight by  $\text{CH}_2$  or  $n$  times  $\text{CH}_2$ . They correspond to the general formula  $\text{C}_n\text{H}_{2n+2}$ . They constitute a homologous series, that is, a series of compounds



so related that when arranged in the order of increasing molecular weights there is a constant difference in composition between successive members.

## PARAFFIN HYDROCARBONS \*

| NAME             | FORMULA                          | MELTING POINT | BOILING POINT | SPECIFIC GRAVITY  |
|------------------|----------------------------------|---------------|---------------|-------------------|
| Methane . . . .  | CH <sub>4</sub>                  | -184°         | -161.4°       | 0.415 (at -161°)  |
| Ethane . . . .   | C <sub>2</sub> H <sub>6</sub>    | -172°         | -88.3°        | 0.546 (at -88°)   |
| Propane . . . .  | C <sub>3</sub> H <sub>8</sub>    | -189°         | -44.5°        | 0.585 (at -44.5°) |
| Butane . . . .   | C <sub>4</sub> H <sub>10</sub>   | -135°         | +0.6°         | 0.600 (at 0°)     |
| Pentane . . . .  | C <sub>5</sub> H <sub>12</sub>   | -131.5°       | 36.3°         | 0.627 (at 14°)    |
| Hexane . . . .   | C <sub>6</sub> H <sub>14</sub>   | -94.3°        | 69.0°         | 0.660 (at 20°)    |
| Heptane . . . .  | C <sub>7</sub> H <sub>16</sub>   | -90°          | 98.4°         | 0.683 (at 20°)    |
| Octane . . . .   | C <sub>8</sub> H <sub>18</sub>   | -56.5°        | 124.6°        | 0.702 (at 20°)    |
| Nonane . . . .   | C <sub>9</sub> H <sub>20</sub>   | -51°          | 150.6°        | 0.718 (at 20°)    |
| Decane . . . .   | C <sub>10</sub> H <sub>22</sub>  | -32°          | 174°          | 0.747 (at 0°)     |
| Undecane . . .   | C <sub>11</sub> H <sub>24</sub>  | -26.5°        | 197°          | 0.773 (at m.p.) ‡ |
| Dodecane . . .   | C <sub>12</sub> H <sub>26</sub>  | -12°          | 216°          | 0.774 (at m.p.)   |
| Tetradecane . .  | C <sub>14</sub> H <sub>30</sub>  | +5.5°         | 252.5°        | 0.775 (at m.p.)   |
| Hexadecane . .   | C <sub>16</sub> H <sub>34</sub>  | 20°           | 287.5°        | 0.775 (at m.p.)   |
| Eicosane . . .   | C <sub>20</sub> H <sub>42</sub>  | 38°           | 205° †        | 0.777 (at m.p.)   |
| Heneicosane . .  | C <sub>21</sub> H <sub>44</sub>  | 40.4°         | 215° †        | 0.778 (at m.p.)   |
| Tricosane . . .  | C <sub>23</sub> H <sub>48</sub>  | 47.4°         | 234° †        | 0.779 (at m.p.)   |
| Hentriacontane . | C <sub>31</sub> H <sub>64</sub>  | 68.1°         | 302° †        | 0.781 (at m.p.)   |
| Hexacontane . .  | C <sub>60</sub> H <sub>122</sub> | 101°          |               |                   |

**Properties.** The saturated hydrocarbons are inert, unreactive, and very stable. The first four members (C<sub>1</sub> to C<sub>4</sub>) are gases at ordinary temperatures and pressures. The next twelve members (C<sub>5</sub> to C<sub>16</sub>) are liquids, and those of still higher molecular weight are solids. The melting points and boiling points become higher as the molecular weights increase. The densities increase in the same order. They are all practically insoluble in water but completely miscible in each other. The gases are odorless; the liquids have odors resembling petroleum, which is a mixture of all of them; and the solids are nearly odorless. All are colorless when pure. The liquid members have a burning taste; the higher members are tasteless.

The saturated hydrocarbons react readily with chlorine and with bromine, but they are attacked very slowly or not at all by other ordinary reagents of the laboratory. Potassium

\*The physical constants included in this table apply to the normal, or straight-chain, compounds.

† At 15 mm. pressure.

‡ m.p. = melting point.

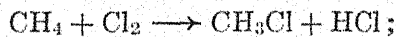


permanganate solution has no effect upon those of low molecular weight, but it does decompose some of the higher members of the series. Concentrated sulfuric acid combines with the solid paraffins, forming sulfonic acids—a hydrogen atom of the hydrocarbon being replaced by the  $\text{SO}_3\text{H}$  group. Concentrated nitric acid acts upon some of the hydrocarbons, replacing a hydrogen atom by the  $\text{NO}_2$  group. They are not affected by sodium hydroxide nor by the free alkali metal. All hydrocarbons burn when heated with air or oxygen. If oxygen is present in abundance, the products of combustion are carbon dioxide and water. Heat alone decomposes the higher hydrocarbons, the products being saturated and unsaturated hydrocarbons of lower molecular weight, and hydrogen.

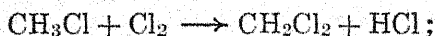
In direct sunlight a mixture of methane and chlorine explodes, with the formation of hydrogen chloride and the deposition of free carbon:



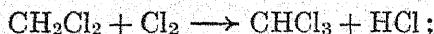
With bromine this reaction does not occur; but fluorine and methane explode when mixed, even in the dark and at low temperatures. Iodine fails to react with any saturated hydrocarbon. In diffused light at low temperatures, and more rapidly as the temperature is raised or the intensity of the light is increased, chlorine and bromine act upon the hydrocarbons, producing substitution products. The action of chlorine on methane is typical and may be represented by the following equations:



Methyl  
chloride



Methylene  
chloride



Chloroform



Carbon  
tetrachloride

Mixed products are obtained when a halogen acts upon a saturated hydrocarbon, for all these reactions occur at the same time. The different possible reactions do not proceed at equal rates, and on this account direct substitution becomes a practical method for making some of the derivatives of methane and its homologues.

The second, third, and fourth reactions shown above are all faster than the first one. As a result of the difference in rates, carbon tetrachloride is the only one of the four possible products that can be obtained in good yield through the direct action of chlorine on methane.

The homologues of methane react with chlorine and bromine in the same way, except that the reaction becomes slower with increasing molecular weight, and in compounds containing more than three carbon atoms it is not possible to remove all the hydrogen by direct substitution.

**Alkyl radicals.** Many different types of compounds may be derived from a saturated hydrocarbon by substituting for hydrogen another element or a group of elements. A relationship between various classes of compounds derived from the hydrocarbons may be seen in the following formulas:

| ALCOHOLS                             | ALKYL CHLORIDES                      | NITRILES                             | ACIDS                                  |
|--------------------------------------|--------------------------------------|--------------------------------------|--|
| $\text{CH}_3\text{OH}$               | $\text{CH}_3\text{Cl}$               | $\text{CH}_3\text{CN}$               | $\text{CH}_3\text{COOH}$               |
| $\text{C}_2\text{H}_5\text{OH}$      | $\text{C}_2\text{H}_5\text{Cl}$      | $\text{C}_2\text{H}_5\text{CN}$      | $\text{C}_2\text{H}_5\text{COOH}$      |
| $\text{C}_3\text{H}_7\text{OH}$      | $\text{C}_3\text{H}_7\text{Cl}$      | $\text{C}_3\text{H}_7\text{CN}$      | $\text{C}_3\text{H}_7\text{COOH}$      |
| $\text{C}_n\text{H}_{2n+1}\text{OH}$ | $\text{C}_n\text{H}_{2n+1}\text{Cl}$ | $\text{C}_n\text{H}_{2n+1}\text{CN}$ | $\text{C}_n\text{H}_{2n+1}\text{COOH}$ |

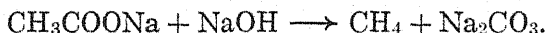
The groups  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ , and so on are found in all classes of aliphatic compounds. These univalent groups, derived from aliphatic hydrocarbons by the removal of one hydrogen atom, are called *alkyl radicals*. They do not exist independently. They occur only in combination with other elements or groups. An alkyl radical is named from the hydrocarbon having the same number of carbon atoms, the termination *ane* being changed to *yl*. Thus  $\text{CH}_3$  is methyl,  $\text{C}_2\text{H}_5$  ethyl,  $\text{C}_3\text{H}_7$  propyl,  $\text{C}_4\text{H}_9$  butyl, and so on. The letter R will be used as a symbol for any alkyl radical, and X will be written as a symbol for any halogen. It will be convenient at times to use general formulas representing classes of compounds instead of specific formulas representing individual members of a class. Thus the formula RI may be used for any alkyl radical combined with iodine, and RX is a general formula for any alkyl radical in combination with any halogen atom.

**Methane.**  $\text{CH}_4$  is a colorless, odorless gas. It burns with a pale blue flame, forming carbon dioxide and water. Only 5.4 cc. of the gas will dissolve in 100 cc. of water at  $0^\circ$ . Its

solubility in alcohol is 52.2 cc. per 100 cc. of the solvent. It forms an explosive mixture with air and has caused many disastrous explosions in coal mines, where it issues from the crevices in the coal seams. The miners call it "fire-damp." Methane is a component of the gases escaping from petroleum and natural gas wells. It is formed wherever vegetable matter decays under water and it constitutes the chief component of marsh gas. It is produced in large quantities in the distillation of coal. The coal gas manufactured for heating and lighting purposes is from 30 to 40 per cent methane. Methane boils at  $-161.4^{\circ}$  and solidifies at  $-184^{\circ}$ . Its critical temperature is  $-82^{\circ}$  and its critical pressure 55 atmospheres.

**Preparation of methane.** Methane may be obtained by the following methods:

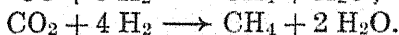
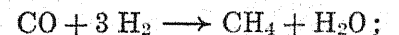
1. By distilling dry sodium acetate with soda lime (a mixture of sodium hydroxide and lime):



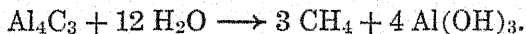
2. By the action of water on methyl magnesium iodide:



3. By heating to  $300^{\circ}\text{C}$ . a mixture of carbon monoxide or carbon dioxide and hydrogen in the presence of finely divided nickel:

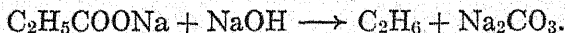


4. By the action of water on aluminum carbide:



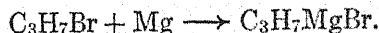
**General methods for preparing hydrocarbons.** The first and second methods listed for the preparation of methane are applications of general reactions.

1. The sodium salt of an acid when distilled with soda lime yields a hydrocarbon with one less carbon atom than was present in the acid. Sodium acetate,  $\text{CH}_3\text{COONa}$ , was used to make methane. To prepare ethane by this method a salt of propionic acid,  $\text{C}_2\text{H}_5\text{COOH}$ , must be used:



The method applies to the formation of all the gaseous and liquid hydrocarbons of the saturated series.

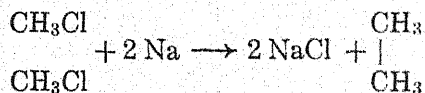
2. An alkyl magnesium halide on hydrolysis yields a hydrocarbon. The reagent is prepared by dissolving metallic magnesium in an ether solution of an alkyl chloride, bromide, or iodide. To prepare propane by this method propyl magnesium halide is employed. The reaction with propyl bromide is represented by the equation



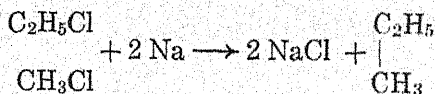
The hydrolysis of this product is accomplished by treatment with cold water:



3. A method devised by Wurtz for building up the higher members from those of lower molecular weight consists in removing halogen atoms from alkyl halides by means of zinc or sodium. The metallic halide is formed and the alkyl radicals unite to form hydrocarbons. For example, chlorine is removed from methyl chloride and the methyl groups combine in pairs to form ethane:



A mixture of ethyl chloride and methyl chloride with sodium yields the next higher member, propane:

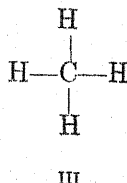
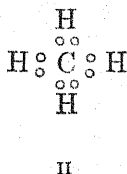
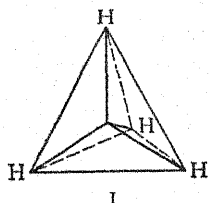


In this case ethane is produced at the same time from pairs of methyl groups, and butane from the union of ethyl radicals. The mixed gases are not easily separated and the method is not a practical one on that account. It is, however, a reaction of great theoretical interest, for it establishes a genetic relationship between the different hydrocarbons.

**Structure and isomerism.** Compounds having the same composition and the same molecular weight, but differing in properties, are called *isomers*. The structure theory accounts for the existence of isomers.

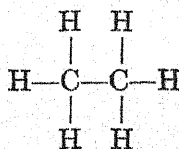
The structure theory is based upon the belief that the four valences of carbon are equal and that these valences are exercised at points corresponding to the apexes of a tetrahedron.

In methane, therefore, the four hydrogen atoms are symmetrically placed with reference to the carbon atom as shown below.

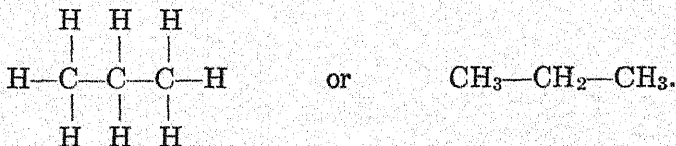


The small circles in formula II represent chemical bonds as pairs of shared electrons. We ordinarily write structural formulas in forms corresponding to II or III, but such formulas are merely projections, on a plane surface, of three-dimensional forms corresponding to type I.

Ethane is derived from methane by the replacement of one of the four similarly placed hydrogen atoms by  $\text{CH}_3$ . It makes no difference which hydrogen is replaced; only one structure is possible for the resulting compound, namely:



This structural formula of ethane is a projection on one plane of a three-dimensional body, supposed to be made up of two tetrahedral carbon atoms attached at one apex of each and holding one hydrogen atom at each of the other six points. Obviously, the six hydrogen atoms in ethane are similarly placed. Each bears the same relation to the molecule as does any other. Substituting a methyl group for one of the hydrogen atoms in ethane results in the formation of propane:

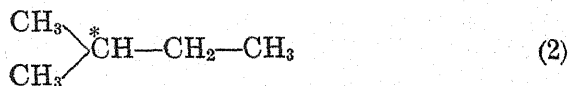
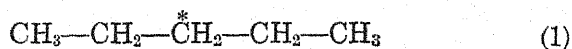


The same process of substitution applied to propane yields butane, but the hydrogen atoms in propane are not all in

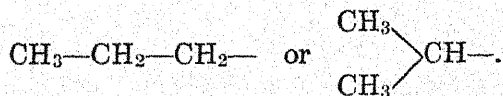


hexanes, nine heptanes, eighteen octanes, thirty-five nonanes, seventy-five decanes, and so on. Not all these possible structures have been built up, for chemists have had more important tasks to perform; but the methods for synthesizing a compound of any given structure have been developed and could, no doubt, be applied in all these cases.

**Nomenclature.** The existence of isomers renders inadequate the system of nomenclature that was outlined above (p. 9). The plan commonly employed is that of naming every paraffin hydrocarbon as a derivative of methane. Just as  $\text{CH}_3\text{Cl}$ ,  $\text{CH}_2\text{Cl}_2$ , and  $\text{CHCl}_2\text{Br}$  would be called chloromethane, dichloromethane, and bromodichloromethane, respectively, so the three pentanes,



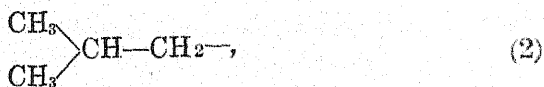
may be named (1) diethyl methane, (2) dimethylethyl methane, and (3) tetramethyl methane. The atoms marked \* are the methane carbon atoms in the structures corresponding to these names. Any carbon atom in the molecule may be chosen as representing the methane residue, and several different names might be applied to the same compound. This causes no confusion, however, for, while a single compound might be known by different names, two different compounds cannot have the same name. If in each of the examples just given we select the next carbon atom to the right of the one marked \* as being the methane carbon, the names become (1) methylpropyl methane, (2) methylisopropyl methane, and (3) tertiary butyl methane. The isomeric forms of the alkyl radicals are distinguished by appropriate names. The propyl group,  $\text{C}_3\text{H}_7-$ , may be



The first is normal propyl and the second isopropyl.

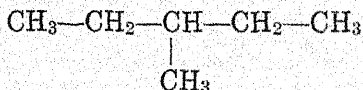


The butyl radical,  $C_4H_9-$ , may have the structures

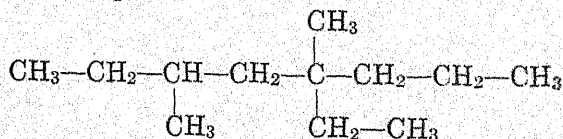


The first is normal butyl (straight chain). The second is isobutyl (branching at the end of the chain as in isopropyl), and the third is tertiary butyl. The carbon having the free valence in (3) is a tertiary carbon atom; that is, it is linked to three other carbon atoms. A carbon atom if linked to two other carbon atoms is called secondary, and if attached to only one other is said to be a primary carbon atom.

In the year 1892 an international congress of chemists assembled in Geneva to devise a uniform and scientific system of nomenclature for chemical compounds. According to the Geneva system a hydrocarbon is named as a derivative of the normal compound corresponding to the longest continuous chain of carbon atoms in the molecule. For example, there are five carbon atoms in the longest continuous chain in the structure



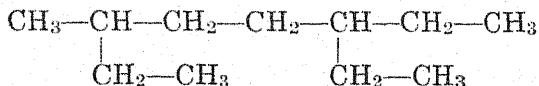
The compound is called 3-methyl-pentane. The numeral 3 placed before the name indicates that the methyl group is attached to the third carbon atom in the pentane chain. A compound having the structure



is called 3-methyl-5-methyl-5-ethyl-octane. The similar groups that are attached to the main chain of atoms may be listed together, making the name 3, 5-dimethyl-5-ethyl-octane. In applying this system it is important to locate the longest continuous chain of carbon atoms. Adherence to this rule avoids



having a single compound listed in the chemical literature under several names. The following compound, for example, should be named 3-methyl-6-ethyl-octane.



It should not be named 2, 5-diethyl-heptane, although this name describes the structure accurately and would be understood as referring to this particular compound. The Geneva system provides for the naming of complex structures of all kinds, but it is beyond the scope of this book to outline the plan in detail. The system is described in Beilstein's "Handbuch der organischen Chemie."

*Petroleum.* The chief natural source of the paraffin hydrocarbons is petroleum. The crude oil usually contains nearly all the members of the series from  $\text{CH}_4$  to  $\text{C}_{27}\text{H}_{56}$  and limited quantities of those of higher molecular weights. Unsaturated hydrocarbons, together with small quantities of compounds containing oxygen, nitrogen, and sulfur, are present also.

The origin of petroleum is unknown. Many theories have been advanced to account for the vast deposits, but no satisfactory explanation has yet been made. Mendelejeff believed that the hydrocarbons were formed by the action of water on metallic carbides. His theory is unsatisfactory, for the composition of petroleum from all sources should be quite uniform if formed in this way. No uniformity exists. Pennsylvania oil is composed almost entirely of paraffin hydrocarbons. Oils from California, Texas, Oklahoma, and Kansas contain anthracene, naphthalene, and other benzene derivatives in addition to paraffins. Russian oils are rich in naphthalene and its homologues.

According to Engler petroleum was formed from the fat of animal tissues. This theory applies especially to oils which contain nitrogen and sulfur compounds. A similar theory, based on the nature of the nitrogen compounds found in petroleum, has been advanced by Mabery.

Petroleum is classified as "paraffin-base" oil if the solid residue is rich in hydrocarbons of the paraffin or methane series. It is known as an "asphaltic-base" oil if in the heavier portions asphalt predominates. Asphalt is a black, solid, hetero-

geneous substance composed largely of polymers of aromatic and aliphatic hydrocarbons and some of their oxidation products. It usually contains sulfur and nitrogen compounds. Asphalt is insoluble in water and in alcohol but it dissolves readily in benzene, acetone, and carbon disulfide. Paraffin and asphalt may be separated by extraction of the former with alcohol.

Crude petroleum varies in color from greenish red to black and varies in specific gravity from 0.76 to 0.98. By distillation it is separated into several fractions. Gasoline is a mixture of hydrocarbons boiling between 50° C. and 225° C. The United States government specifications for gasoline are as follows:

| DISTILLATION                         | TEMPERATURE   |
|--------------------------------------|---------------|
| First drop in the receiver . . . . . | Not over 55°  |
| 20 % in the receiver . . . . .       | Not over 105° |
| 50 % in the receiver . . . . .       | Not over 140° |
| 90 % in the receiver . . . . .       | Not over 200° |
| Final boiling point . . . . .        | Not over 225° |

The corresponding temperature range for kerosene is approximately 150° C. to 300° C. In actual practice the gasoline range is determined by specific-gravity measurements and not by reference to boiling points. Lubricating oil, paraffin wax, and vaseline are mixtures of hydrocarbons of high molecular weight. They are obtained from petroleum. At high temperatures the higher hydrocarbons decompose with the production of paraffins and olefins of lower molecular weight. The production of low-boiling hydrocarbons from the higher-boiling fractions of petroleum is called a "cracking" process. The manufacture of gasoline by thermal decomposition of higher-boiling fractions is an important commercial activity. Gasoline produced by the cracking process differs in some respects from that obtained in the ordinary distillation of crude oil. It is characterized by the presence of a higher percentage of unsaturated compounds.

*Shale.* In many localities there are large deposits of soft brown or gray shale containing complex carbon compounds. At dull red heat the crushed rock yields its organic matter in the form of gaseous and liquid hydrocarbons, paraffin, and ammonia. The crude mixture of hydrocarbons is refined by distillation, as in the case of petroleum. Hydrocarbon oils are

not present as such in shale. They are formed from more complex carbon compounds during the process of distillation. The yield of oil obtainable from shale varies from zero to ninety gallons per ton. The richest and most extensive deposits in the United States are in Colorado, Utah, Wyoming, and Montana. The distillation of shale for fuel oil has been an established commercial industry in France and Scotland since 1850.

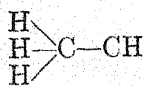
### THE ETHYLENE SERIES

Ethylene,  $C_2H_4$ , a gas with a faint, sweet odor, was named by the early chemists olefiant (oil-forming) gas because it combines with chlorine and bromine, forming oily liquid products. Hydrocarbons derived from ethylene, corresponding in composition to the general formula  $C_nH_{2n}$ , are called olefins or alkylenes. The members of this series differ in many ways from the saturated hydrocarbons. They combine with chlorine and bromine by direct addition, forming halogen derivatives without loss of hydrogen. Each hydrocarbon in this series contains two less hydrogen atoms than the saturated hydrocarbon having the same number of carbon atoms. Theoretically the first member of the series should be methylene,  $CH_2$ , but this has never been isolated. The simplest known olefin is ethylene,  $C_2H_4$ .

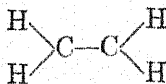
### ETHYLENE HYDROCARBONS

| NAME                                 | FORMULA                  | BOILING POINT  |
|--------------------------------------|--------------------------|----------------|
| Ethylene . . . . .                   | $CH_2=CH_2$              | $-103.8^\circ$ |
| Propylene . . . . .                  | $CH_3-CH=CH_2$           | $-47^\circ$    |
| Butylene                             |                          |                |
| Ethylethylene . . . . .              | $C_2H_5-CH=CH_2$         | $-18^\circ$    |
| Sym. dimethylethylene . . . . .      | $CH_3-CH=CH-CH_3$        | $+1.4^\circ$   |
| Isobutylene . . . . .                | $(CH_3)_2C=CH_2$         | $-6^\circ$     |
| Amylene                              |                          |                |
| Normal propylethylene . . . . .      | $CH_3-CH_2-CH_2-CH=CH_2$ | $+40^\circ$    |
| Isopropylethylene . . . . .          | $(CH_3)_2CH-CH=CH_2$     | $20.1^\circ$   |
| Sym. methylethylethylene . . . . .   | $CH_3-CH=CH-C_2H_5$      | $36.4^\circ$   |
| Unsym. methylethylethylene . . . . . | $(CH_3)(C_2H_5)C=CH_2$   | $32^\circ$     |
| Trimethylethylene . . . . .          | $(CH_3)_2C=CH-CH_3$      | $38.4^\circ$   |
| Hexylene (normal) . . . . .          | $C_4H_9-CH=CH_2$         | $64.1^\circ$   |
| Heptylene (normal) . . . . .         | $C_5H_{11}-CH=CH_2$      | $99^\circ$     |
| Octylene (normal) . . . . .          | $C_6H_{13}-CH=CH_2$      | $123^\circ$    |
| Decylene (normal) . . . . .          | $C_8H_{17}-CH=CH_2$      | $172^\circ$    |

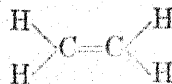
There are three possible structures for ethylene:



I



II

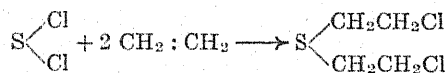


III

In formula I the unsaturated condition of the molecule is represented by a carbon atom attached to only two other atoms. Such a compound would be a bivalent free radical and its addition product with chlorine would be  $\text{CH}_3 \cdot \text{CHCl}_2$ , both chlorine atoms being attached to the same carbon atom. By the action of phosphorus pentachloride on acetaldehyde,  $\text{CH}_3 \cdot \text{CHO}$ , the oxygen of the aldehyde is replaced by two chlorine atoms, yielding a product with this structure. It bears very little resemblance to the addition product formed from ethylene and chlorine. The latter, therefore, must have one chlorine atom attached to each of the two carbon atoms, and formula I must be abandoned. Formula II represents each carbon atom as trivalent. If carbon can exist in stable compounds in the trivalent state, there is no logical explanation for the fact that whenever an unsaturated compound forms an addition product with hydrogen or a halogen or with any other reagent it does so by combining with two atoms of hydrogen or of a halogen or, in general, with two equivalents of the atoms or ions of the reagent used. Since addition always involves a pair of atoms, ions, or radicals, we must conclude that formula II is unsatisfactory. Formula III represents two carbon atoms linked to each other by a double bond, two of the four valences on each carbon atom being exercised in holding carbon to carbon. The activity of such a molecule is attributed to the strain involved in bringing the relatively fixed valence positions near enough together to admit of such a union. Addition of a halogen is interpreted, on the basis of this formula, as due to breaking the double bond, thereby allowing each of the carbon atoms to hold a halogen atom. The structure of the chlorine addition product formed with ethylene then becomes  $\text{CH}_2\text{Cl} \cdot \text{CH}_2\text{Cl}$ , a structure that is in harmony with all known methods for its preparation.

Ethylene was made in large quantities during the war of 1914-1918. It was used in the manufacture of the very poisonous  $\beta$ - $\beta$ -dichloroethyl sulfide, commonly called mustard gas. The compound is an oily liquid

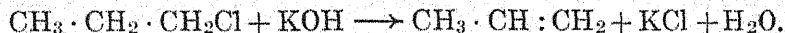
(b.p. 216°, f.p. 14°). Its vapor, when inhaled, acts as a slow but certain poison. It penetrates the skin also and produces serious burns. It is formed by passing ethylene gas into a solution of sulfur dichloride in carbon tetrachloride:



Unsaturated compounds are quite susceptible to oxidation by permanganates and by dichromates, whereas the saturated hydrocarbons are not affected by these reagents. When mixed with oxygen or air, and ignited, the saturated hydrocarbons burn at least as readily as do the unsaturated compounds of approximately the same molecular weight. The heat of combustion of ethylene is greater than the heat of combustion of an equivalent quantity of free carbon and hydrogen, indicating a negative heat of formation for this hydrocarbon.

**Preparation.** Hydrocarbons of the ethylene series may be prepared by the following methods:

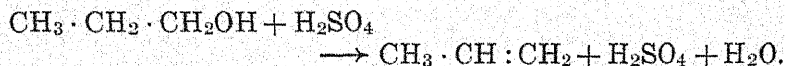
1. An alkyl halide, when heated with an alcoholic solution of potassium hydroxide, yields a molecule of hydrogen halide and an unsaturated hydrocarbon. The hydrogen and halogen are taken from adjacent carbon atoms and a double bond is thus established:



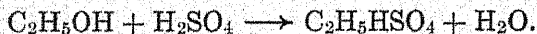
2. Dihalogen derivatives of the paraffin hydrocarbons having the two halogen atoms attached to different, but adjacent, carbon atoms yield unsaturated hydrocarbons when warmed with zinc or sodium:



3. Alcohols may be dehydrated by means of sulfuric acid or phosphorus pentoxide:

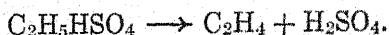


This reaction proceeds in two steps. In the first place an alkyl derivative of sulfuric acid is formed. With ordinary ethyl alcohol and sulfuric acid the reaction takes the following course:



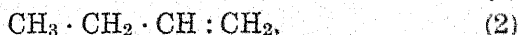
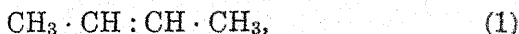
Ethyl sulfuric acid,  $\text{C}_2\text{H}_5\text{HSO}_4$ , is an oily liquid. It is not

isolated from the excess of sulfuric acid or alcohol when ethylene is the product wanted. The mixture containing this compound is heated to about  $170^{\circ}$  and the second step in the process is accomplished:



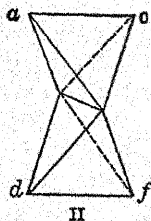
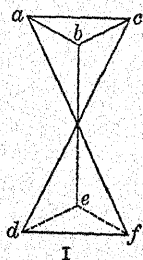
The commercial production of ethylene is accomplished by passing alcohol vapor over clay balls or aluminum oxide in an iron tube heated to  $400^{\circ}$ .

**Isomerism.** Isomerism arises from changes in the configuration of the molecule either by branching of the carbon chains or by changing the position of the double bond. There are three possible structures for butylenes and three are actually known:



The first is produced by the action of alcoholic potash on secondary butyl iodide,  $\text{CH}_3 \cdot \text{CHI} \cdot \text{CH}_2 \cdot \text{CH}_3$ . The second is obtained in the same way from normal butyl iodide,  $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2\text{I}$ . The third has been made by the action of sulfuric acid on isobutyl alcohol,  $(\text{CH}_3)_2\text{CH} \cdot \text{CH}_2\text{OH}$ .

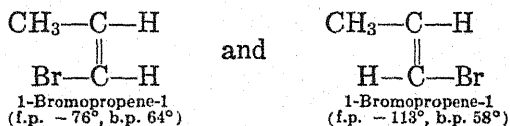
There is a type of isomerism, displayed by unsaturated compounds only, which is due to the relatively rigid union between atoms that share a double bond. Carbon atoms united by a single bond may rotate independently around their common axis, but a double bond between two atoms prevents free rotation. Single and double bonds between carbon atoms may be represented graphically as follows:



The tetrahedra attached at one point only (I) are free to

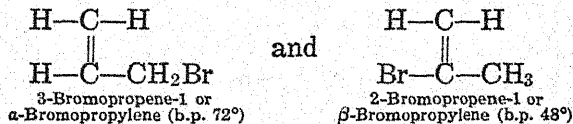
rotate around their common axis so that *a* may be placed over *d*, *e*, or *f*, but tetrahedra attached to each other by two points (II) (having one edge in common) are not free to turn independently, and hence the geometrical figure produced when the double bond is established cannot be altered without breaking the connection at one point or the other. A certain amount of energy must be supplied to break the double bond and enable the molecule to assume a new configuration, and, as a result of this energy requirement, the unsaturated molecules are stable enough to appear in isomeric forms. To distinguish this kind of isomerism from other types of structural variations it is called *geometrical isomerism*.

As an example of geometrical isomerism we have two bromopropylenes corresponding to the formula  $\text{CH}_3\text{—CH=CHBr}$ .



In one of these structures the two hydrogen atoms are on the same side of the molecule (*cis* form). In the other the two hydrogen atoms are on opposite sides of the molecule (*trans* form). Either of these compounds can be converted into a mixture of the two forms by the application of heat. In other words, when the necessary activation energy is supplied, the double bond is broken and the molecule exists for a short interval in a condition that permits reestablishment of the bond either in the original position or in a position that produces the opposite configuration in the molecule.

Two other bromopropylenes are known, corresponding to the structures



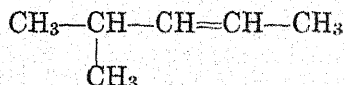
These compounds are not geometrical isomers.

More important examples of geometrical isomerism (*cis-trans* isomerism) will be considered later.

**Nomenclature.** The name of an olefin is commonly derived from the name of the paraffin hydrocarbon having the same

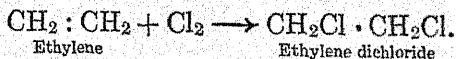


number of carbon atoms by changing the termination *ane* to *ylene*; thus,  $C_3H_6$  is propylene,  $C_4H_8$  butylene,  $C_5H_{10}$  amylene or pentylene. This system, however, is inadequate, for it does not provide distinctive names for all isomers. The olefins may be named as derivatives of ethylene, just as the saturated hydrocarbons were named as derivatives of methane. Referring to the butylenes listed on page 24, the names are (1) symmetrical dimethylethylene, (2) ethylethylene, (3) unsymmetrical dimethylethylene. According to the Geneva system they are named from the number of carbon atoms in the longest straight chain by changing the termination of the name of the corresponding paraffin from *ane* to *ene*. The position of the double bond is indicated by a number specifying the location of the first doubly linked carbon atom in the chain. This number may follow the suffix *ene* or precede the name referring to the number of carbon atoms in the continuous chain. It is customary to begin the numbering at the end nearest the double bond. Several names could be applied to the following compound:



The names in common use are 4-methyl-pentene-2 and 4-methyl-2-pentene.

**Reactions of the ethylene series.** Sulfuric, hydrobromic, hydriodic, hypobromous, and hypochlorous acids form addition products with the alkylenes. The halogens likewise combine with unsaturated hydrocarbons by direct addition. With chlorine or bromine the reaction proceeds to completion:

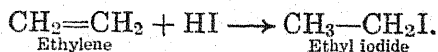


Diffused light is used to catalyze the union of ethylene and bromine. The addition of chlorine to ethylene occurs in the dark but much more rapidly in the light, and the rate of the reaction increases as the temperature is lowered. Substitution reactions occur to some extent when chlorine and ethylene are mixed, as shown by the evolution of small quantities of hydrogen chloride. The rates of the substitution reactions become slower as the temperature is reduced. When ethylene is passed into an aqueous solution of chlorine, various products,



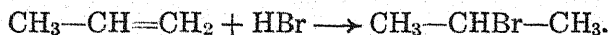
besides ethylene dichloride, are formed in small amounts. Hypochlorous acid as well as chlorine is present in such a solution, and both are good oxidizing agents. There are other reagents, which, under special conditions, may be used to break the double bond. Among these are hydrogen chloride, nitrosyl chloride, sulfur chlorides, and ozone.

Hydrobromic acid and hydriodic acid readily combine with ethylene and its homologues:



Hydrogen chloride slowly forms an addition product with an olefin when the two reagents are heated together in the presence of glacial acetic acid.

When compounds that ionize react with unsymmetrical derivatives of ethylene, the negative ion usually goes to the carbon atom which is holding the fewer hydrogen atoms, that is, the more completely substituted carbon atom of the doubly linked pair. Hydrobromic acid, for example, combines with propylene as follows:



This rule, formulated by Markownikoff,\* may be used to predict the structure of the main product formed in an addition reaction as ordinarily carried out in the laboratory, but in nearly every case an isomeric compound, formed by addition in the reverse order, is a by-product. Kharasch and his colleagues found that in the presence of peroxides the mode of addition usually is the reverse of that which would be expected under the Markownikoff rule.† We shall encounter other exceptions to the rule when we study conjugated systems of double bonds.

When hypochlorous acid or hypobromous acid reacts with an unsaturated hydrocarbon, under ordinary conditions, the hydroxyl group becomes attached to the carbon atom holding the fewer hydrogen atoms:

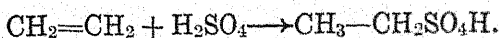


\* Waldemar Markownikoff was professor of chemistry in the University of Moscow from 1873 to 1890.

† Kharasch and Mayo, *J. Am. Chem. Soc.*, 55, 2468 (1933). See also *J. Org. Chem.* 2, 288 (1937).

This result has led many to suppose that in acids of this type the electrons are so distributed as to make the halogen positive with respect to the hydroxyl group. In aqueous solution an acid of the type HOX yields the ions  $H^+$  and  $OX^-$ , but in forming an addition product with an unsaturated compound it supplies OH and X to the unsaturated carbon atoms. The mechanism of the reaction is not fully understood.

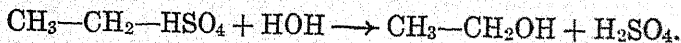
Ethylene dissolves in concentrated sulfuric acid with the formation of ethyl sulfuric acid:



Ethyl sulfuric acid (ethyl hydrogen sulfate) is an oily liquid. It dissolves in water but is not readily hydrolyzed by water alone nor by an acid solution. Hydrolysis is accomplished by heating an alkaline solution of the compound. The barium salt of ethyl hydrogen sulfate is soluble in water, and this property is used in separating the ester from unchanged sulfuric acid.

The mixture of ethyl hydrogen sulfate and sulfuric acid is diluted with water and treated with an excess of barium carbonate. The precipitate of barium sulfate and the undissolved excess of barium carbonate are removed together by filtration. The barium salt of the ethyl sulfuric acid is contained in the filtrate. The filtrate is reduced to smaller volume by partial evaporation of the water. The residue is then cooled by packing the container in ice, and from the cold solution barium ethyl sulfate crystallizes with two molecules of water. The salt is decomposed with the calculated quantity of sulfuric acid, and the precipitated barium sulfate is removed by filtration. Finally the free ethyl sulfuric acid is obtained by evaporation of the water over phosphorus pentoxide in a vacuum desiccator.

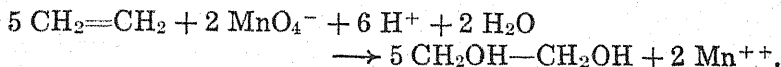
The product formed through the union of an olefin and concentrated sulfuric acid may be hydrolyzed by boiling it with a solution of sodium hydroxide. An alcohol is produced:



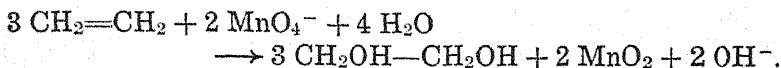
The addition of sulfuric acid to an olefin is especially applicable to the hydrocarbons of low molecular weight. Other members of the series, when treated with sulfuric acid, yield mixed products, including unsaturated compounds and polymers of high molecular weights and unknown structures.

An olefin may be oxidized to a dihydric alcohol (an OH group being added to each of the two unsaturated carbon atoms), but unless the reaction is carefully controlled the oxidation proceeds

beyond this stage. The conversion of ethylene into glycol through the agency of permanganate ion in acid solution is represented by the equation

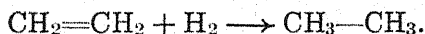


In alkaline solution a similar reaction occurs, but manganese dioxide instead of a manganous salt is formed:



In this process hydroxide ions are produced in a solution originally alkaline. It is an irreversible process, and it is catalyzed by hydroxide ions. An alkaline solution of a permanganate is generally used to oxidize an unsaturated hydrocarbon when the addition of a hydroxyl group to each of the unsaturated carbon atoms is desired.

When the vapor of an unsaturated hydrocarbon is mixed with hydrogen gas and the mixture is passed over hot, finely divided nickel, a saturated hydrocarbon is formed:



The reduction of liquid unsaturated hydrocarbons can be accomplished generally by treatment with concentrated hydriodic acid and red phosphorus or through the direct action of hydrogen gas in contact with finely divided nickel or platinum.

### THE ALLYLENE SERIES

Members of the allylene series of hydrocarbons are represented by the general formula  $\text{C}_n\text{H}_{2n-2}$ . This is also the general formula for members of the acetylene group. The allylenes, or diolefins, have two double bonds in each molecule. The isomeric acetylene hydrocarbons are characterized by the presence of a triple bond in each molecule.

The simplest diolefin is allylene,  $\text{CH}_2=\text{C}=\text{CH}_2$ , a colorless gas that liquefies under atmospheric pressure at  $-32^\circ$ . The most useful diolefins possess conjugated systems of double bonds, that is, the two double bonds are removed from each other by one single bond attachment. A bond structure of the type  $>\text{C}=\text{C}-\text{C}=\text{C}<$  is present in all conjugated systems, but such systems are not limited to chains of carbon atoms. Many

compounds possessing this series of alternate double and single bonds polymerize readily. Polymerization is a process in which two or more molecules of the same kind unite.

A diolefin is named with reference to the longest continuous chain of carbon atoms in the molecule. The presence of two double bonds is indicated by the suffix *diene* and the positions of the double bonds are denoted by numerals. The first carbon atom involved in each multiple linkage is specified in the name. Thus,  $\text{CH}_3\text{—CH=CH—CH=CH—CH}_3$  is called 2, 4-hexadiene.

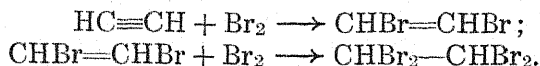
*Isoprene* (2-methyl-1, 3-butadiene) is a colorless liquid which boils at  $34^\circ$ . It is the principal product formed when pure, unvulcanized rubber is decomposed by heat. A polymer of isoprene can be made by warming the liquid with metallic sodium. The sodium acts as a catalyst in this condensation process and it is possible in this way to convert isoprene into a polymer of very high molecular weight — several hundred molecules uniting. The product closely resembles natural rubber, and like ordinary rubber it yields isoprene when subjected to destructive distillation. The product formed when isoprene polymerizes is believed to consist of a long, continuous chain of isoprene units.

A more useful source of artificial rubber is *chloroprene*; 2-chloro-1, 3-butadiene,  $\text{CH}_2=\text{CCl—CH=CH}_2$ . This is a colorless liquid (b.p.  $59.4^\circ$ ) which polymerizes much more readily than does isoprene. Artificial rubber made from chloroprene is on the market under the trade name of Duprene. The polymerization of chloroprene can be controlled. A gummy substance closely resembling crude rubber may be made or a harder product similar to vulcanized rubber may be produced. The plastic form may be mixed with pigments and fillers, as in the treatment of natural rubber, and the mixture may then be rendered tough and elastic by heating for a short time at a temperature slightly above  $100^\circ$ .

### THE ACETYLENE SERIES

Hydrocarbons of the acetylene series correspond to the general formula  $\text{C}_n\text{H}_{2n-2}$ , and in each molecule there is a triple bond between carbon atoms. The reasons for assigning to this formula a triple linkage between carbon atoms rather than assuming bivalent carbon or free valence bonds are similar

to those mentioned in the discussion of ethylene. Addition products are readily formed, univalent elements or groups invariably adding in pairs. Bromine, for example, absorbs acetylene, forming dibromoethylene and tetrabromoethane.



The reaction takes place in two stages and can be regulated by using an aqueous solution of bromine so as to yield the intermediate product, dibromoethylene,  $\text{CHBr}:\text{CHBr}$ . The addition is catalyzed by light.

*Acetylene* is a colorless gas, almost insoluble in water but very soluble in acetone. At  $15^\circ$ , under 1 atmosphere of pressure one volume of acetone dissolves twenty-five volumes of the gas. The solubility increases rapidly as the pressure is increased or the temperature reduced. At  $-80^\circ$  and 12 atmospheres of pressure the solubility is greater than 2000:1. Acetylene is an endothermic compound, the molecular heat of formation being  $-54$  Cal. ( $-54,000$  cal.). It decomposes, therefore, with a liberation of energy, and when under two or more atmospheres of pressure it can be detonated by mercury fulminate or by an electric spark.

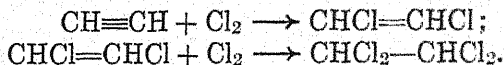
In an open container acetylene burns with a smoky flame, but when used in a properly constructed burner the flame is white, smokeless, and rich in rays of short wave length. The high temperature of the oxygen-acetylene flame gives the gas a technical value in welding processes. Iron is easily melted in the flame. Explosive mixtures of acetylene and air can be made with the proportions of the hydrocarbon varying from 3 per cent to 82 per cent, an unusually wide range. This property affords an explanation of the many explosions that have occurred in houses lighted by acetylene. Most other hydrocarbons, when mixed with air, burn quietly at the outlet if the air content of the mixture is below 50 per cent. The velocity of propagation of combustion is higher for acetylene than for other gases. This gives rise to a very sudden development of pressure and makes it unsafe to explode a mixture of acetylene and air even in an open flask.

When acetylene is passed into a vigorously stirred suspension of mercuric sulfate in dilute sulfuric acid, it is converted into acetaldehyde,  $\text{CH}_3\text{CHO}$ . The result accomplished

is the addition of a molecule of water to the unsaturated hydrocarbon. The course of the reaction probably involves the addition of sulfuric acid, this step being followed by hydrolysis. Commercial applications of this process have been made for the production of acetic acid, acetone, and other compounds that are easily derived from acetaldehyde.

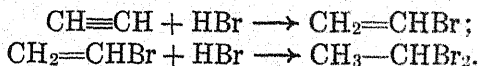
Reactions of the acetylene series. The following reactions of acetylene are typical for members of this series:

1. By the addition of chlorine or bromine, substituted olefins and saturated halogen compounds are formed:

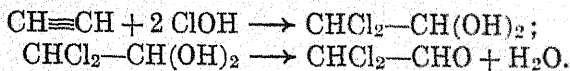


Light catalyzes this reaction. The union of iodine and acetylene is accomplished by keeping the acetylene for some time in contact with a pasty mixture of iodine and alcohol.

2. Hydrogen bromide and hydrogen iodide slowly form derivatives of the olefins and finally unsymmetrical saturated dihalogen compounds:



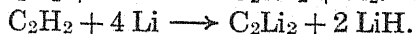
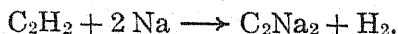
3. Hypochlorous and hypobromous acids combine with acetylene hydrocarbons, forming aldehydes:



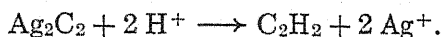
The addition product having two hydroxyl groups on the same carbon atom is unstable and cannot be isolated. Water is eliminated and a stable aldehyde is formed.

4. Hydrogen attached to a carbon atom which, in turn, is linked to another carbon by a triple bond may be replaced by a metal. Silver acetylide is precipitated when acetylene gas is led into an ammoniacal solution of a silver salt. It is a white crystalline solid which explodes when agitated. Its formula is  $\text{Ag}-\text{C}\equiv\text{C}-\text{Ag}$ . Copper acetylide is a red explosive solid formed by passing acetylene gas into a solution of cuprous chloride in ammonia. The property of forming insoluble silver or copper derivatives distinguishes the compounds having the group  $-\text{C}\equiv\text{CH}$  from all other hydrocarbons. Sodium and

lithium carbides are formed when acetylene is passed into the molten metals. Free hydrogen or the hydride of the metal is simultaneously produced :



Similar compounds may be prepared by the direct action of carbon on many metals at temperatures attainable in the electric furnace. These carbides are easily decomposed by acids. Silver acetylide, for example, dissolves in a dilute solution of an acid, with the evolution of acetylene :

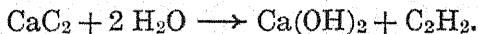


5. The acetylene hydrocarbons are reduced to the corresponding saturated compounds by heating them with hydrogen in contact with platinum black or finely divided nickel.

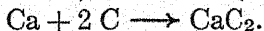
6. An alkaline permanganate solution oxidizes acetylene to a salt of oxalic acid :



**Preparation of acetylene.** 1. Acetylene is usually made by allowing water to drop on calcium carbide. The reaction is very energetic and must be carefully controlled to avoid excessive pressure in the generator :



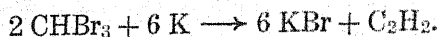
Calcium carbide is manufactured on a commercial scale by heating a mixture of lime and coke at  $2500^\circ$  to  $3000^\circ \text{C}$ . in an electric furnace. Metallic calcium combines with carbon directly at a much lower temperature to form the same product ; but a high temperature is required to reduce the calcium oxide. The mechanism of the process is indicated by two equations :



2. Acetylene is formed from the free elements in an electric arc between carbon poles in an atmosphere of hydrogen. Equilibrium is attained (at  $2500^\circ$ ) with less than 4 per cent of acetylene present. Traces of other hydrocarbons are formed at the same time.

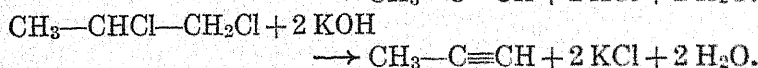
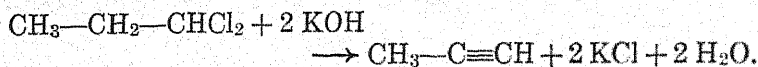


3. Chloroform, bromoform, and iodoform yield their halogen atoms to molten sodium or potassium, the CH residues uniting in pairs to form acetylene:



The higher members of the acetylene series are prepared by the following general methods:

**Preparation of homologues of acetylene.** 1. Dihalogen derivatives of the saturated hydrocarbons having the two halogen atoms attached to the same or to adjacent carbon atoms are treated with alcoholic potash:



Compounds having two double bonds (diolefins) are contaminating by-products when the method indicated by the last equation is used.

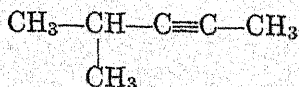
2. Tetrahalogen compounds having two halogens attached to each of two adjacent carbon atoms yield acetylene derivatives when warmed with sodium or distilled with zinc dust:



**Nomenclature.** Hydrocarbons containing triple bonds may be named as derivatives of acetylene. Thus  $\text{CH}_3\text{—C}\equiv\text{CH}$  is

methyl acetylene;  $\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{CH—C}\equiv\text{C—CH}_2\text{—CH}_3$  is ethyliso-

propyl acetylene; and so on. According to the Geneva plan the name is derived from the number of carbon atoms in the longest continuous chain. The name terminates in *ine*, and the position of the triple bond is indicated by a number following the name of the compound or preceding that part of the name which refers to the continuous chain. A compound having the structure



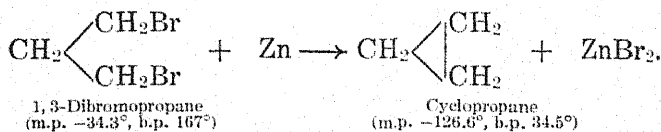
is called 4-methyl-pentine-2, or 4-methyl-2-pentine. Numbering begins at the end nearest the triple bond.



## THE ALICYCLIC SERIES

Hydrocarbons of the ethylene series were represented by the general formula  $C_nH_{2n}$ . The same general formula must be assigned to another series of hydrocarbons known as cycloparaffins or polymethylenes. In these compounds the carbon chains are in the form of closed rings. They are referred to, therefore, as *cyclic* compounds, and since in chemical properties they are more like aliphatic than aromatic compounds, they are called *alicyclic* hydrocarbons.

*Cyclopropane.* The first member of the group is known as cyclopropane. It is a gas which can be liquefied at ordinary temperatures by placing it under five or six atmospheres of pressure. Cyclopropane is present in small quantities in the gases that escape from petroleum wells. It can be produced synthetically by warming 1, 3-dibromopropane with zinc dust.



The reverse process (the conversion of cyclopropane into 1, 3-dibromopropane) is accomplished by treating the hydrocarbon with bromine. In forming an addition product with bromine cyclopropane displays a property of the unsaturated hydrocarbons, but the higher members of this series of hydrocarbons do not form addition products at ordinary temperatures. A three-membered ring of atoms is not very stable, and this compound is more reactive than its homologues. At a temperature as low as  $75^\circ$  cyclopropane reacts with hydrogen if the mixed gases are in contact with finely divided nickel or platinum. The reduction product is propane. The catalytic reduction of cyclobutane to normal butane is accomplished at  $120^\circ$ , and higher members of the series resist the action of hydrogen and nickel.

*Cyclopentane* and *cyclohexane* occur together in crude petroleum. They correspond to the following structural formulas:

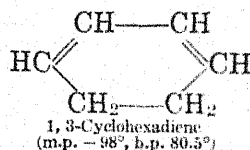
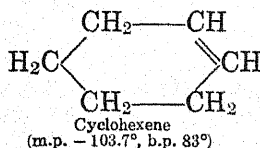


Many derivatives of cyclohexane are found in the fragrant volatile oils occurring in some plants and trees. Eucalyptus, pine, and citrus trees, as well as mint, geranium, and lemon grass, yield compounds related to this hydrocarbon.

## CYCLOPARAFFINS

| NAME                             | FORMULA    | DENSITY *            | MELTING POINT | BOILING POINT |
|----------------------------------|------------|----------------------|---------------|---------------|
| Cyclopropane, trimethylene . .   | $(CH_2)_3$ | 0.720 <sup>-79</sup> | - 126.6°      | - 34.5°       |
| Cyclobutane, tetramethylene . .  | $(CH_2)_4$ | 0.703 <sup>-0</sup>  | - 50°         | 13.0°         |
| Cyclopentane, pentamethylene . . | $(CH_2)_5$ | 0.751                | - 93.3°       | 49.5°         |
| Cyclohexane, hexamethylene . .   | $(CH_2)_6$ | 0.779                | 6.5°          | 81.4°         |
| Cycloheptane, heptamethylene . . | $(CH_2)_7$ | 0.810                | - 12°         | 118.1°        |
| Cyclooctane, octamethylene . .   | $(CH_2)_8$ | 0.839                | 14.4°         | 150.6°        |

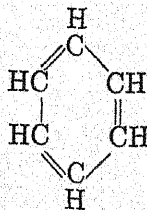
Only brief mention will be made, at this point, of the *unsaturated* cyclic hydrocarbons. Cyclohexene and cyclohexadiene are represented by the following formulas:



Cyclohexatriene, better known as benzene, is one of the most important compounds in the realm of chemistry. It is briefly described in the following section.

## THE BENZENE SERIES

Although benzene is not an *aliphatic* hydrocarbon it must be mentioned here, for we shall have to deal with some of its derivatives very soon. Benzene has the formula  $C_6H_6$  and the six carbon atoms constitute a closed chain or ring. The structural formula for the compound is written as follows:



\* Density at 20° unless otherwise specified.

Benzene is a colorless liquid which boils at 80.4°. It is produced in the destructive distillation of bituminous coal. It is a pure hydrocarbon and must not be confused with the commercial product sold under the name of *benzine* (called also petroleum ether), which is a mixture of several aliphatic hydrocarbons, including pentane, hexane, and other members of the methane series.

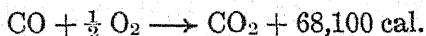
The radical  $C_6H_5-$ , known as the *phenyl* group, is derived from benzene just as the methyl group,  $CH_3-$ , is derived from methane. The phenyl radical, like the methyl radical, has not been isolated, but it exists in combination with many other groups and atoms. We have, for example, such compounds as phenyl bromide,  $C_6H_5Br$ ; phenyl chloride,  $C_6H_5Cl$ ; phenyl cyanide,  $C_6H_5CN$ ; benzoic acid,  $C_6H_5COOH$ ; and phenol,  $C_6H_5OH$ . A systematic study of the derivatives of benzene will be undertaken later.

### THERMOCHEMICAL RELATIONS

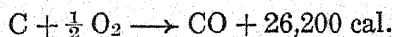
The total energy change involved in passing from a definite initial state to a definite final state is independent of the path. We may apply this principle in calculating the heats of formation of organic compounds. Carbon dioxide may be formed directly from carbon and oxygen with the energy change indicated in the equation



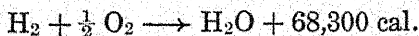
It may be made also by burning carbon monoxide as indicated by the equation



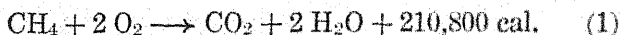
The difference between these energy values represents the energy change involved in forming one mole of carbon monoxide:



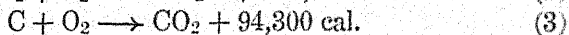
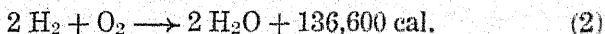
In the same way we may calculate the heats of formation of the hydrocarbons. Water and carbon dioxide are the products formed in the complete oxidation of a hydrocarbon; and we need, in addition to the data given above, the heat of formation of water



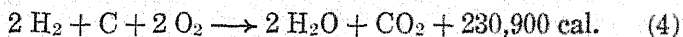
The heat of formation of a substance represents the difference in energy content between one mole of the compound and an equal quantity of the uncombined elements. As a rule stable compounds are formed from the elements with an evolution of heat (loss of energy), but some compounds are formed with an absorption of energy. One mole of methane burns in oxygen, forming carbon dioxide and water with an evolution of 210,800 cal.:



For the uncombined elements we have



Adding equations (2) and (3), we have



Subtracting (1) from (4),



This represents the energy used in breaking up the molecule when methane burns, or it is the heat that would be evolved if methane were made by direct union of carbon and hydrogen.

On the other hand, some of the lower members of the unsaturated hydrocarbons burn with the evolution of more heat than is derived from equivalent weights of the free elements. In other words, they have negative heats of formation.

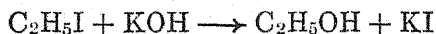
#### HEAT OF COMBUSTION

|                   |              |                     |              |
|-------------------|--------------|---------------------|--------------|
| Methane . . . . . | 210,800 cal. | Ethylene . . . . .  | 332,000 cal. |
| Ethane . . . . .  | 368,400 cal. | Propylene . . . . . | 490,000 cal. |
| Propane . . . . . | 526,300 cal. | Butylene . . . . .  | 650,200 cal. |
| Butane . . . . .  | 682,300 cal. | Acetylene . . . . . | 312,000 cal. |

# ALCOHOLS

## SATURATED MONOHYDRIC ALCOHOLS

The saturated monohydric alcohols may be regarded as derivatives of the paraffin hydrocarbons in which one hydrogen atom in each molecule has been replaced by a hydroxyl group. The general formula for alcohols of this series is  $C_nH_{2n+1}OH$ , or  $ROH$ . An alcohol may be prepared from an alkyl halide by treatment with an aqueous solution of a base. Prolonged boiling of the mixture is generally necessary.

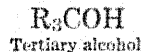
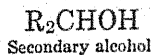
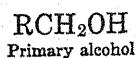


Sodium hydroxide and amyl chloride are used in the commercial process of making amyl alcohol. Other general methods for making alcohols will be presented later. The first two members of the series, methyl alcohol and ethyl alcohol, are of great commercial importance, and special means have been devised to produce them in vast quantities at comparatively low cost.

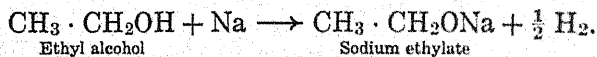
**Physical properties.** The alcohols of low molecular weight are colorless liquids. The first three members of the series are miscible with water in all proportions. The members of the group containing from four to eleven carbon atoms are oily liquids sparingly soluble in water. The solubilities decrease as the molecular weights increase. The higher members are colorless solids, almost tasteless and odorless, and practically insoluble in water. They are readily soluble in the liquid members of the series, and from these solutions some of them may be obtained in crystalline form.

**Classification.** Alcohols are classified as primary, secondary, and tertiary. The classification is based upon the number of carbon atoms that are bound by the carbon which is directly attached to the hydroxyl group. Every primary alcohol is characterized by the group  $-CH_2OH$ , while secondary and tertiary alcohols have the groups  $\text{>CHOH}$  and  $\text{>COH}$  respectively.

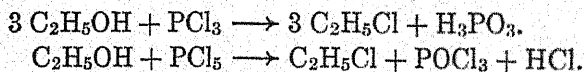
General formulas may be written as follows :



**Chemical properties.** 1. Alcohols react with metallic sodium or potassium with the evolution of hydrogen, but only one hydrogen atom in each molecule of a monohydric alcohol is replaceable by the metal. This fact is used in establishing the presence of a hydroxyl group in the alcohol molecule. For example, two structures are possible for a compound having the formula  $\text{C}_2\text{H}_6\text{O}$ . We might write it  $\text{CH}_3 \cdot \text{O} \cdot \text{CH}_3$  or  $\text{CH}_3 \cdot \text{CH}_2\text{OH}$ . In the first formula the six hydrogen atoms are all similarly placed. If one is replaceable by a metal, there is no apparent reason why two, three, or even six should not be replaced by the same reagent. In the second formula five of the hydrogen atoms are attached directly to carbon and one is held by oxygen. The formula indicates that one hydrogen atom differs from all the others in its relation to the molecule as a whole, and since in ethyl alcohol one and only one hydrogen atom is replaced by sodium, we assign to it the second formula and write the following equation for the reaction :

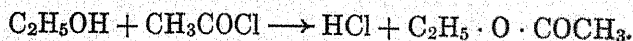


2. Alcohols react with phosphorus trichloride or phosphorus pentachloride, forming alkyl halides :



These reactions confirm the conclusion that an alcohol molecule contains a hydroxyl group. A univalent chlorine atom replaces an atom of oxygen and one of hydrogen — a change easily explained under the assumption that the oxygen and hydrogen are present in the form of a univalent group.

3. Acid chlorides and alcohols yield esters :



This reaction is discussed under acid chlorides (see page 94).

4. Alcohols are susceptible to oxidation. Chromic acid converts ethyl alcohol into acetaldehyde, and by the same reagent it is further oxidized to acetic acid. On account of

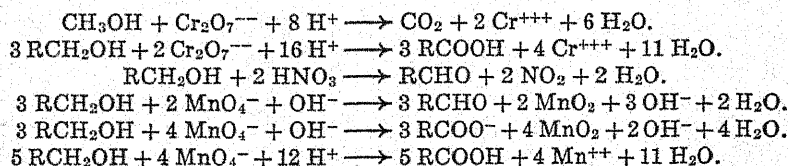
its volatility free acetaldehyde is obtained unless precautions are taken to prevent its escape from the reaction mixture:



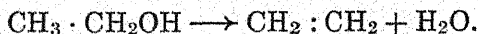
Primary, secondary, and tertiary alcohols may be differentiated by identifying the types of compounds formed from them by oxidation. A primary alcohol is converted into an aldehyde having the same number of carbon atoms as in the alcohol molecule. The aldehyde, in turn, is oxidized to an acid without loss of carbon. A secondary alcohol is oxidized to a ketone having the same number of carbon atoms, but on further oxidation the ketone yields carbon dioxide and water or acids containing fewer carbon atoms than the ketone itself possessed. A tertiary alcohol is decomposed at once by oxidation to compounds of lower molecular weight.

Tertiary alcohols are not as readily oxidized as are the primary and secondary compounds. On the other hand, the replacement of the hydroxyl group by a halogen through the agency of a phosphorus halide, or its removal in the formation of water by a dehydrating agent, proceeds with greater ease with tertiary than with primary or secondary alcohols.

The products formed in the oxidation of an alcohol depend upon the reagents used, the character of the alcohol, and the temperature of the reaction. Some typical reactions are shown below. These equations must not be interpreted as meaning that different oxidizing agents necessarily form different products when they act upon an alcohol. The list is intended merely to indicate several possible results.



5. Alcohols are dehydrated by the action of concentrated sulfuric acid, hydrocarbons of the ethylene series being formed:



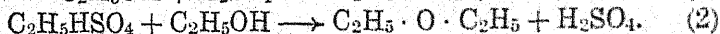
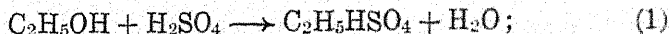
The reaction proceeds even more readily with secondary and tertiary alcohols. By modifying the conditions (controlling the temperature and the concentration of the acid) one molecule



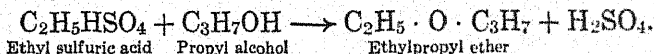
of water may be removed from two molecules of alcohol, with the production of an ether :



An intermediate product, in this case ethyl sulfuric acid, is formed between the alcohol and acid; but it is decomposed by the excess of alcohol, regenerating the acid and forming the ether. The mechanism of the formation of diethyl ether is indicated in the following equations :



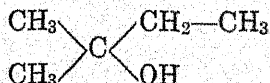
Mixed ethers may be secured by mixing sulfuric acid with the calculated quantity of one alcohol to produce an ester according to (1) and gradually adding another alcohol during the process of distillation. Reaction (2) then occurs with the second alcohol :



Ethyl sulfuric acid    Propyl alcohol

Ethylpropyl ether

**Nomenclature.** According to the Geneva system, an alcohol is named as a derivative of the hydrocarbon having the same number of carbon atoms in the longest continuous chain. The name is made to terminate in *ol*. The position of a radical, substituted for hydrogen, is indicated by a numeral preceding the name of the radical. The position of the hydroxyl group is shown by a number following the suffix *ol* (original Geneva plan) or by a number immediately preceding the class name (modified Geneva plan). A compound having the structure



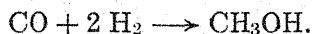
is called 2-methyl-butanol-2 or 2-methyl-2-butanol.

*Methyl alcohol* (wood alcohol),  $\text{CH}_3\text{OH}$ , is a colorless liquid (sp. gr. 0.792 at  $20^\circ$ ; b. p.  $64.6^\circ$ ). It burns with a nonluminous flame forming carbon dioxide and water. It has a burning taste and is poisonous. It is an excellent solvent for many types of organic compounds. It is now commonly called methanol, but it was at one time known as carbinol.

Methyl alcohol is obtained on a commercial scale from wood by dry distillation. Among the products found in the distillate are water, acetic acid, methyl alcohol, acetone, and tar. The

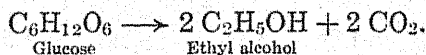
tar settles out on standing, and the liquid layer is siphoned off, treated with lime and water, then redistilled. The lime converts the acetic acid into a nonvolatile salt, calcium acetate, and the water throws out of solution hydrocarbons and some other compounds which can be separated by mechanical means from the aqueous solution of methyl alcohol and acetone. By fractional distillation most of the water is eliminated. Quicklime,  $\text{CaO}$ , is employed to complete the dehydration of the distillate. The methyl alcohol and acetone may be separated by treatment with calcium chloride, which absorbs methyl alcohol.

A process for making methyl alcohol from carbon monoxide and hydrogen has been developed. The possibility of obtaining methyl alcohol in this way was realized more than a hundred years ago, but the conditions under which the reaction could be made commercially profitable were not discovered until 1925. The reaction is represented by the equation



The gases, in contact with a suitable catalyst, are heated to temperatures ranging from  $300^\circ$  to  $400^\circ$  under pressures of 150 to 350 atmospheres. The effective catalysts are mixtures of metallic oxides at least one of which must not be reduced by hydrogen under the working conditions. A mixture composed of oxides of zinc, copper, and aluminum is commonly employed.

*Ethyl alcohol.* By fermentation glucose is converted into ethyl alcohol and carbon dioxide:



Fermentation is induced by an enzyme, zymase, found in yeast. The fermentation of fruit juices for the production of wine is mentioned in the Bible and in other ancient writings. Leeuwenhoek, as early as 1683, described the microscopic appearance of yeast, but it was first definitely characterized as a plant by Tour in 1836. A few years later Pasteur connected fermentation with the life processes of the yeast plant. He considered the conversion of sugar into alcohol and carbon dioxide to be dependent upon the life and growth of the yeast in the sugar solution. This theory prevailed until Büchner (1897) showed that an extract from yeast containing no living cells could cause fermentation (see Enzymes, page 182).

Starch is the commercial source of the glucose used in the manufacture of alcohol. Potatoes, corn, wheat, or rice may be used as sources of starch. Enzymes contained in sprouting barley have the property of catalyzing the hydrolysis of starch, converting it into fermentable sugars.

Ground corn is mixed with water and heated an hour or more with steam under about 3 atmospheres of pressure. After cooling, malt is added and the mixture is held at 63° C. until the starch has been completely hydrolyzed. The iodine test for starch is made from time to time until a sample of the mixture no longer gives the characteristic blue color of starch iodide. The husks of the grain are removed by forcing the mash through a coarse filter. The portion passing through the sieve or filter is conveyed to the fermentation vats. Yeast is added and the temperature is held between 20° and 25° C. until the conversion of sugar to alcohol is complete. This part of the process requires from three to five days. The mash then consists of a slimy fluid mixture of water, alcohol, fusel oil, traces of organic acids and aldehydes, and a solid residue of the grain. From this mixture the alcohol is obtained by distillation. It is not possible to secure absolute alcohol from an aqueous solution of alcohol by distillation alone. A mixture containing 95.5 per cent alcohol and 4.5 per cent water has a maximum vapor pressure, and this mixture distills without change in composition at 78.17° C.\* In the preparation of absolute alcohol the ordinary 95 per cent product is dehydrated by boiling it, under a reflux condenser, with calcium oxide (quicklime). The water is retained by the lime, and the alcohol is liberated from the semisolid mass by distillation.

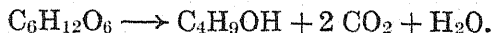
*Butyl alcohols.* Normal butyl alcohol has the formula



It is an excellent solvent for many types of organic compounds. It combines with acetic acid, forming an ester, normal butyl acetate, which is a valuable component of the fine lacquers that are used on automobiles. Normal butyl alcohol is a colorless liquid that boils at 117.7° and has a specific gravity of 0.805 at 25° C. One volume of the alcohol dissolves in ten volumes of water, but it is miscible in all proportions with ethyl alcohol and with ether.

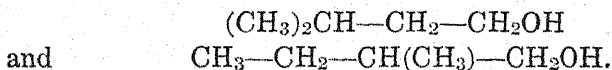
\* Noyes and Warfel, *J. Am. Chem. Soc.*, 23, 463 (1901).

A fermentation process has been developed for making the alcohol from sugars derived from starch. The reaction proceeds according to the equation



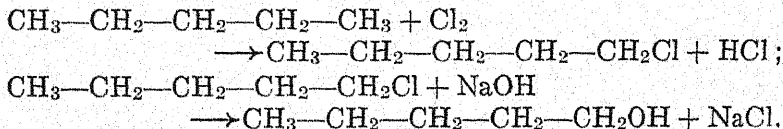
Isobutyl alcohol,  $(\text{CH}_3)_2\text{CH}-\text{CH}_2\text{OH}$ , is found with amyl alcohols in fusel oil. It can be separated from the amyl alcohols by fractional distillation. It is formed as a by-product in the synthesis of methyl alcohol from carbon monoxide and hydrogen. Isobutyl alcohol is used as a source of many types of compounds containing the isobutyl radical that are required in research laboratories. No important uses have been found for the secondary and tertiary butyl alcohols.

*Amyl alcohols.* The alcohols corresponding to the empirical formula  $\text{C}_5\text{H}_{11}\text{OH}$  are known as amyl alcohols. The name was first applied to two members of the group,



These alcohols constitute the major part of the fusel oil formed as a by-product when ethyl alcohol is made from starch. The word "amyl" is derived from the Greek name for starch. We believe now that these alcohols are derived from the proteins found in corn, wheat, rice, or potatoes and not from the starch, but they are still called amyl alcohols.

Amyl alcohols are manufactured in enormous quantities for industrial uses. The free alcohols and also amyl acetates, made from amyl alcohols and acetic acid, are used as solvents for gums, resins, and nitrocellulose in the manufacture of lacquers. The alcohols are made from the pentanes derived from natural gas or gasoline. The pentanes are chlorinated by treatment with free chlorine, and the chloropentanes are hydrolyzed to amyl alcohols by hot aqueous solutions of sodium hydroxide.\*



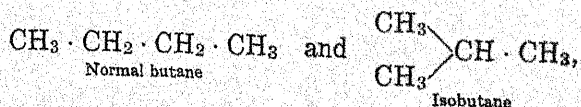
\* For a description of the factory process operating upon a scale that involves the use of twenty-two tons of chlorine per day, see Eugene E. Ayers, *J. Ind. and Eng. Chem.*, 21, 899 (1929). Read also M. M. Wilson and F. J. Worster, *J. Ind. and Eng. Chem.*, 21, 592 (1929).

These equations represent the formation of normal amyl alcohol. Other amyl alcohols are formed at the same time, for not all the chlorine enters the pentane molecule on the terminal carbon atom. A mixture of the isomeric pentanes is generally used, and this is another cause for the production of mixed alcohols. Some dichloro derivatives of the pentanes are formed in the chlorination process; and if these are not removed from the monochloro derivatives before treatment with the hot sodium hydroxide solution, the amyl alcohols formed are contaminated with dihydric alcohols.

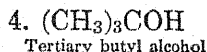
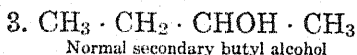
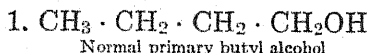
## SATURATED MONOHYDRIC ALCOHOLS

| NAME                               | FORMULA  | MELTING POINT | BOILING POINT | SPECIFIC GRAVITY AT 20° |
|------------------------------------|--|---------------|---------------|-------------------------|
| Methyl alcohol . . . . .           | CH <sub>3</sub> OH   | -97.8°        | +64.6°        | 0.792                   |
| Ethyl alcohol . . . . .            | CH <sub>3</sub> -CH <sub>2</sub> OH  | -117.3°       | 78.5°         | 0.789                   |
| Propyl alcohols                    |  |               |               |                         |
| Normal propyl . . . . .            | CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> OH                                   | -127°         | 97.8°         | 0.804                   |
| Isopropyl . . . . .                | CH <sub>3</sub> -CHOH-CH <sub>3</sub>  | -85.8°        | 82.3°         | 0.786                   |
| Butyl alcohols                     |  |               |               |                         |
| Normal primary . . . . .           | CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> OH                  | -89.8         | 117.7°        | 0.810                   |
| Normal secondary . . . . .         | CH <sub>3</sub> -CHOH-CH <sub>2</sub> -CH <sub>3</sub>                                 | Glass         | 99.5°         | 0.808                   |
| Isobutyl . . . . .                 | (CH <sub>3</sub> ) <sub>2</sub> CH-CH <sub>2</sub> OH                                  | -108°         | 107.3°        | 0.802                   |
| Trimethyl carbinol . . . . .       | (CH <sub>3</sub> ) <sub>3</sub> COH  | +25.5°        | 82.8°         | 0.789                   |
| Amyl alcohols                      |  |               |               |                         |
| Normal primary . . . . .           | CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> OH | -78.5°        | 138°          | 0.817                   |
| Isobutyl carbinol . . . . .        | (CH <sub>3</sub> ) <sub>2</sub> CH-CH <sub>2</sub> -CH <sub>2</sub> OH                 | -117.2°       | 131°          | 0.812                   |
| Secondary butyl carbinol . . . . . | CH <sub>3</sub> -CH(C <sub>2</sub> H <sub>5</sub> )-CH <sub>2</sub> OH                 | —             | 128°          | 0.816                   |
| Methylpropyl carbinol . . . . .    | CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CHOH-CH <sub>3</sub>                | —             | 118°          | 0.810                   |
| Diethyl carbinol . . . . .         | C <sub>2</sub> H <sub>5</sub> -CHOH-C <sub>2</sub> H <sub>5</sub>                      | —             | 115.6°        | 0.822                   |
| Methylisopropyl carbinol . . . . . | (CH <sub>3</sub> ) <sub>2</sub> CH-CHOH-CH <sub>3</sub>                                | —             | 114°          | 0.819                   |
| Dimethylethyl carbinol . . . . .   | (CH <sub>3</sub> ) <sub>2</sub> COH-C <sub>2</sub> H <sub>5</sub>                      | -12°          | 102°          | 0.809                   |
| Tertiary butyl carbinol . . . . .  | (CH <sub>3</sub> ) <sub>3</sub> C-CH <sub>2</sub> OH                                   | +53°          | 114°          | —                       |
| Higher alcohols                    |  |               |               |                         |
| Normal hexyl . . . . .             | C <sub>6</sub> H <sub>13</sub> OH  | -51.6°        | 155.8°        | 0.820                   |
| Normal heptyl . . . . .            | C <sub>7</sub> H <sub>15</sub> OH  | -34.6°        | 176°          | 0.821                   |
| Normal octyl . . . . .             | C <sub>8</sub> H <sub>17</sub> OH  | -16.5°        | 194°          | 0.827                   |
| Normal nonyl . . . . .             | C <sub>9</sub> H <sub>19</sub> OH  | -5°           | 215°          | 0.828                   |
| Normal decyl . . . . .             | C <sub>10</sub> H <sub>21</sub> OH   | +7°           | 231°          | 0.829                   |

**Isomerism.** There are more isomeric alcohols corresponding to a given empirical formula than there are hydrocarbons having the same number of carbon atoms; for isomerism may be due not only to a branching of the carbon chain but also to a change in the position of the hydroxyl group, or to both of these causes. There are, for example, two butanes,



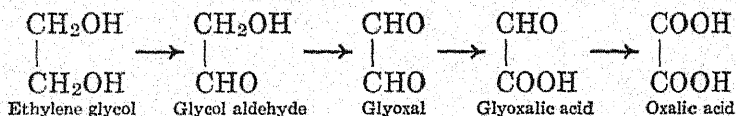
and four butyl alcohols:



### POLYHYDRIC ALCOHOLS

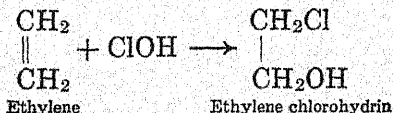
Polyhydric alcohols are characterized by the presence, in each molecule, of two or more hydroxyl groups. With few exceptions these groups are so distributed that not more than one is held by any single carbon atom. Many reactions are known which might be expected to place two or three hydroxyl groups on the same carbon atom; but almost invariably these reactions lead to the formation of acids, aldehydes, or ketones.

The dihydric alcohols are known as glycols. They are soluble in water and boil at higher temperatures than the corresponding monohydric alcohols. They form two series of esters with acids, yield monosodium and disodium derivatives, and on oxidation give rise to a variety of products corresponding to different stages in the oxidation process. It is not always practical to isolate all the intermediate products. Ethylene glycol, for example, is converted to oxalic acid through the following steps:



Glyoxal and glyoxalic acid, however, are never made by direct oxidation of the alcohol.

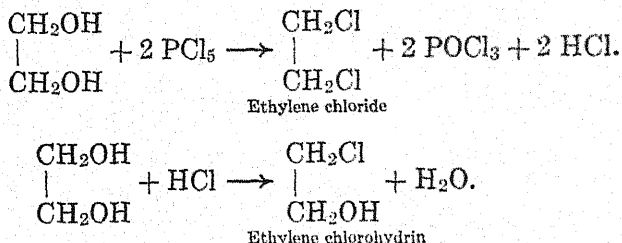
*Ethylene glycol*,  $\text{CH}_2\text{OH}-\text{CH}_2\text{OH}$ , is a sweet, colorless liquid that melts at  $-12.3^\circ$  and boils at  $197.2^\circ$ . It is used as an "anti-freeze" liquid in automobile radiators, as a solvent in the manufacture of nitrocellulose lacquers, and in the preparation of a class of explosives known as nitroglycols. It is prepared from ethylene and hypochlorous acid. These reagents combine to form ethylene chlorohydrin:





The chlorohydrin (b.p.  $128^{\circ}$ ) is hydrolyzed by warming it to  $70^{\circ}$  with a dilute solution of sodium bicarbonate. There is a steady evolution of carbon dioxide until the reaction is completed.

Phosphorus pentachloride and phosphorus trichloride act upon ethylene glycol, substituting chlorine for both hydroxyl groups, but hydrogen chloride gas acts upon one hydroxyl group only:



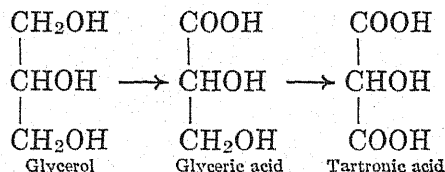
Hydrogen chloride is split off from ethylene chlorohydrin by sodium or potassium hydroxide, and ethylene oxide is formed. Ethylene oxide (b.p.  $14^{\circ}$ ) reacts rapidly with hydrochloric acid, regenerating ethylene chlorohydrin, or with water to form glycol, or with hydrogen (in contact with platinum black) to form ethyl alcohol.

*Glycerol*, or glycerine,  $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CH}_2\text{OH}$ , a trihydric alcohol, is obtained from fats and oils. Fats are hydrolyzed by boiling them with acids or alkalies, by the action of enzymes, or by treatment with superheated steam. In the latter process the fat is placed in an autoclave and subjected to the action of steam at  $315^{\circ} \text{C.}$  for several hours. The glycerol liberated is purified by distillation in a partial vacuum. It is a heavy, oily, viscous liquid. It is miscible with water in all proportions and has a sweet taste. It melts at  $17^{\circ} \text{C.}$  and boils at  $290^{\circ} \text{C.}$  It is formed when sugar undergoes alcoholic fermentation, the quantity produced varying from 1 to 3 per cent of the weight of the sugar.

Glycerol is used in the manufacture of inks, confectionery, and many pharmaceutical preparations. Its most valuable compounds are the natural and artificial esters in which glycerol is combined with acids. The important esters of glycerol occurring in nature are the animal and vegetable fats and oils. The chief artificial preparation is nitroglycerine.



A mixture of glycerol and solid potassium permanganate takes fire spontaneously. In aqueous solution the rate of the reaction can be controlled, and tartronic acid is produced. Mercuric oxide converts glycerol into glyceric acid.



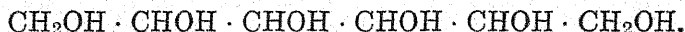
Glyceric acid is a sirupy liquid which does not crystallize. Tartronic acid crystallizes in large colorless prisms that melt at  $158^\circ$ . Both are soluble in water and alcohol, and both decompose below  $200^\circ$ .

*Erythritol*,  $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CHOH} \cdot \text{CH}_2\text{OH}$ , a tetrahydric alcohol, occurs in many seaweeds. It is a sweet crystalline solid (m.p.  $126^\circ$ , b.p.  $332^\circ$ ). Erythritol is reduced by hydrogen iodide to normal secondary butyl iodide,  $\text{CH}_3 \cdot \text{CHI} \cdot \text{CH}_2 \cdot \text{CH}_3$ . This result indicates that in erythritol the carbon atoms constitute a normal, or continuous, chain.

*Arabitol* and *xylitol* are isomeric pentahydric alcohols. *Arabitol* is a crystalline substance melting at  $103^\circ$ . *Xylitol* is a sirupy liquid. Both are soluble in water, and their solutions are sweet. They are obtained by reducing the sugars, arabinose and xylose. They are both represented by the formula



*Mannitol*, *dulcitol*, and *sorbitol* are isomeric hexatomic alcohols:

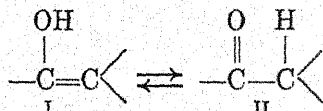


They are obtained by reducing sugars that have corresponding structures. Mannitol occurs in manna, the sap of certain species of ash. It is extracted from manna with hot alcohol, from which it crystallizes on cooling.

The most important polyhydric alcohols are those that have the carbonyl group ( $-\text{CO}-$ ) in addition to hydroxyl groups. They are aldehydes or ketones as well as alcohols. The sugars belong to this group. They are considered in the chapter on Carbohydrates.

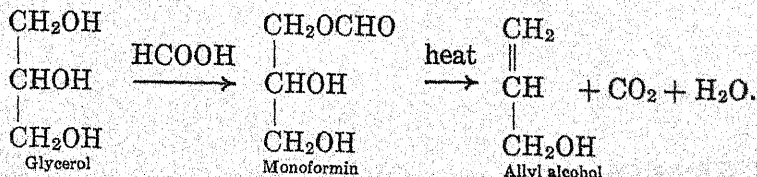
## UNSATURATED ALCOHOLS

The unsaturated alcohol corresponding to the simplest possible structure,  $\text{CH}_2=\text{CHOH}$ , has not been prepared. All attempts to produce it have resulted in the formation of acetaldehyde,  $\text{CH}_3-\text{CHO}$ . The hydroxyl group is rarely held by carbon which is attached by two bonds to another carbon atom. Such compounds are, no doubt, produced in numerous reactions, but an immediate intramolecular rearrangement gives rise to the more stable form. The essential feature of the rearrangement may be outlined as follows:



The hydroxyl hydrogen atom migrates from oxygen to the adjacent unsaturated carbon atom, breaking the double bond between the carbon atoms and establishing it between carbon and oxygen. Compounds containing structure I are called enols. (A hydroxyl group is held by a carbon atom, which, in turn, is linked by a double bond to another carbon atom.) Structure II is characteristic of aldehydes and ketones. In some cases this reaction is reversible and an equilibrium is established between the unsaturated alcohol and the aldehyde or ketone. This type of reversible change in structure is called keto-enol tautomerism.

*Allyl alcohol*,  $\text{CH}_2=\text{CH}-\text{CH}_2\text{OH}$ , a colorless liquid (b.p.  $96.6^\circ$ , sp. gr. 0.872), is prepared by heating glycerol with oxalic acid. Oxalic acid is decomposed by heat into formic acid and carbon dioxide. Formic acid,  $\text{HCOOH}$ , and glycerol form an ester called monoformin, but at temperatures higher than  $215^\circ$  the ester decomposes into carbon dioxide, water, and allyl alcohol. At a lower temperature and in the presence of water monoformin is readily hydrolyzed to formic acid and glycerol.



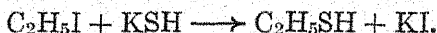
According to the structure theory three different allyl alcohols might exist, namely,  $\text{CH}_2=\text{CH}-\text{CH}_2\text{OH}$ ,  $\text{CH}_2=\text{COH}-\text{CH}_3$ , and  $\text{CHOH}=\text{CH}-\text{CH}_3$ . Only the first is known. The second and third formulas show the attachment of a hydroxyl group to an unsaturated carbon atom. If the second compound were formed, it would rearrange to  $\text{CH}_3-\text{CO}-\text{CH}_3$ , a stable substance known as acetone; and the third would change to propionaldehyde,  $\text{CHO}-\text{CH}_2-\text{CH}_3$ .

Allyl alcohol readily forms an addition product with chlorine or bromine. It is oxidized by silver oxide to acrolein,  $\text{CH}_2=\text{CH}-\text{CHO}$ , and to acrylic acid,  $\text{CH}_2=\text{CH}-\text{COOH}$ .

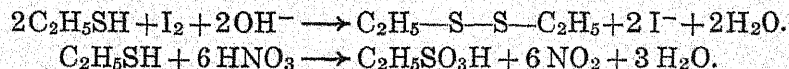
*Propargyl alcohol*,  $\text{HC}\equiv\text{C}-\text{CH}_2\text{OH}$ , is a colorless liquid boiling at  $115^\circ$ . It forms explosive metallic derivatives corresponding to the silver and copper salts of acetylene. With chlorine and bromine the unsaturated alcohols form addition products.

### MERCAPTANS

The mercaptans are related to hydrogen sulfide in the same way that alcohols are related to water. Ethyl mercaptan (b.p.  $36^\circ$ ) is formed by heating in an autoclave an alcoholic solution of ethyl iodide and potassium hydrogen sulfide just as alcohol is made from ethyl iodide and potassium hydroxide:



Mercaptans may be made by heating alcohols with phosphorus pentasulfide or by passing a mixture of hydrogen sulfide and alcohol vapor over hot thorium oxide. The mercaptans are colorless liquids, slightly soluble in water, and characterized by disagreeable odors. Sodium mercaptide,  $\text{C}_2\text{H}_5\text{SNa}$ , crystallizes in colorless needles. It is prepared by dissolving sodium in an ether solution of ethyl mercaptan. It is extensively hydrolyzed in aqueous solution. Mercury mercaptide,  $(\text{C}_2\text{H}_5\text{S})_2\text{Hg}$ , is only slightly soluble in water. It crystallizes from alcohol in leaflets melting at  $86^\circ$ . Mercaptans are oxidized to disulfides by iodine and an alkali. Nitric acid converts them into sulfonic acids:

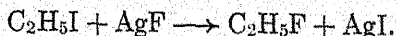


## ALKYL HALIDES AND PARAFFIN POLYHALIDES

If we adhere to the common practice of classifying organic compounds as derivatives of the hydrocarbons, we may define an alkyl halide as a compound which is derived from a saturated hydrocarbon through the substitution of a halogen atom for a hydrogen atom. The general formula for such a compound is  $RX$ . Actually the alkyl halides are usually made from alcohols by substituting a halogen atom for the hydroxyl group. When we speak of a compound as a derivative of a hydrocarbon we do not mean that the compound is necessarily made from the hydrocarbon; the statement merely emphasizes a structural relationship that exists between the compound under consideration and a hydrocarbon.

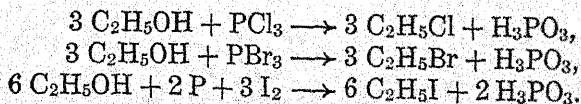
Many alkyl chlorides and bromides are made directly from the corresponding hydrocarbons by treatment with chlorine and bromine respectively, but the process gives rise to a mixture of substitution products. The reaction does not stop when one hydrogen atom has been replaced, and it is not always easy to separate the products formed. (See the equations representing reactions between methane and chlorine, p. 11.)

The reaction of fluorine on a hydrocarbon cannot be controlled with sufficient certainty to make it a profitable method for the production of an alkyl fluoride. The reaction always leads to the formation of large amounts of free carbon. Indirect methods are used in making alkyl fluorides. Silver fluoride and an alkyl iodide may be used for this purpose:

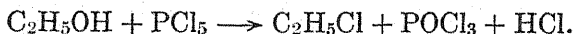


No important industrial uses have been found for the alkyl fluorides.

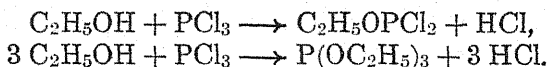
Alkyl chlorides, bromides, and iodides may be prepared through the action of a phosphorus halide on an alcohol:



Phosphorus pentachloride may be substituted for the trichloride:

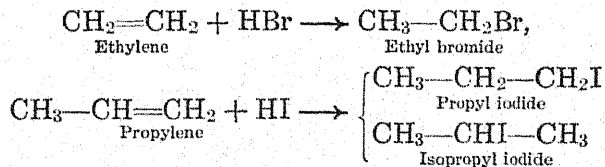


Alcohols and phosphorus halides are capable of reacting in more than one way, and products not indicated by the above equations are formed. This is especially true when phosphorus trichloride is used. Typical reactions are represented by the following equations:



When the same reagents are capable of yielding different products it is the task of the chemist to find conditions that favor the desired reaction.

An alkyl chloride, bromide, or iodide may be made through the addition of the proper hydrogen halide to an unsaturated hydrocarbon:



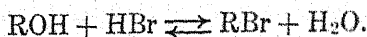
Hydrogen chloride does not form an addition product with an unsaturated hydrocarbon as readily as does hydrogen bromide or hydrogen iodide. The rate of addition of a halogen acid is faster with the higher members of the series of unsaturated hydrocarbons than with ethylene.

Alkyl chlorides, bromides, and iodides may be made through the action of a halogen acid on an alcohol:



This reaction proceeds smoothly with HI, and less readily with HBr. When HCl is the acid employed it is usually necessary to add a catalyst ( $\text{ZnCl}_2$ ) and to heat the mixture in an autoclave or in a sealed tube. The halogen acids react more readily with tertiary alcohols than with primary compounds. The reaction between an alcohol and a halogen acid is a reversible process. If the mixture is heated in a sealed tube to prevent the

escape of volatile products, an equilibrium is established between the reagents and the products formed:



A reversible reaction reaches equilibrium when the rate of transformation in one direction is exactly equal to the rate of change in the reverse order. Representing the molal concentration of the alcohol by  $a$ , that of the acid by  $b$ , and the moles per liter of alkyl halide and water by  $c$  and  $d$ , respectively, equilibrium is established when  $\frac{cd}{ab} = k$ . For every reversible reaction there is a definite numerical value of  $k$ , the equilibrium constant, which can be determined experimentally. With  $k$  known, the equation affords a means of estimating the quantity of each product that will be formed from any given mixture.

At the beginning of the reaction indicated above,  $c$  and  $d$  are equal to zero and the reaction proceeds from left to right only. As soon as  $c$  and  $d$  reach finite values the reverse reaction begins, and it continues with increasing velocity as the product  $cd$  increases. The velocity of the forward reaction is retarded as the product  $ab$  diminishes, until the value of  $k$  is reached. If  $x$  is the number of moles of ROH transformed in time  $t$ , it is also the number of moles of HX used, and the velocity constant,  $k_1$ , is given by the differential equation

$$\frac{dx}{dt} = k_1(a - x)(b - x).$$

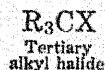
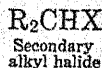
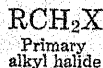
The rate of change in the reverse order is

$$-\frac{dx}{dt} = k_2(c + x)(d + x).$$

The apparent rate of change in either direction at any instant is the difference between the rates of the two opposing reactions, and at equilibrium the apparent rate of change is zero. The system has not reached a static condition, however. Both reactions are going on, but with equal velocities. The equilibrium constant,  $k$ , is a ratio between the velocity constants of the opposing reactions:

$$k = \frac{k_1}{k_2}.$$

The alkyl halides are classified as primary, secondary, and tertiary compounds. The general formulas are as follows:



**Properties.** Methyl chloride, ethyl chloride, and methyl bromide are gases under ordinary conditions of temperature and pressure. All other alkyl halides included in the table on page 56 are liquids; the higher members are solids. In each group the densities decrease as the molecular weights increase.

In other words, the specific gravity of an alkyl halide is roughly proportional to the per cent of halogen in the molecule. The alkyl halides are almost insoluble in water, but they dissolve readily in alcohol, ether, benzene, and other organic solvents. They do not ionize as pure liquids nor in solution, yet they take part in many types of reactions that involve the removal of the halogen and substitution of other elements or groups. Most of these reactions are slow, incomplete, and reversible. There is a lack of uniformity in the behavior of these compounds. Ethyl iodide, for example, reacts promptly with silver nitrate, yielding a precipitate of silver iodide. Alkyl iodides of higher molecular weights either fail to react with silver ions or do so very slowly. Alkyl halides are hydrolyzed to alcohols by prolonged boiling with *aqueous* potassium hydroxide. A hot concentrated *alcoholic* solution of potassium hydroxide converts an alkyl halide into an unsaturated hydrocarbon if the structure of the halide permits the removal of hydrogen and halogen from adjacent carbon atoms.

A halogen derivative of an unsaturated hydrocarbon in which the halogen is attached to a saturated carbon atom acts like an alkyl halide in so far as the behavior of the halogen atom is concerned. Allyl bromide,  $\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$ , 3-bromopropene-1, a liquid boiling at  $71^\circ$ , is derived from allyl alcohol and phosphorus tribromide. It is hydrolyzed to allyl alcohol by aqueous alkalis and responds to all the reactions that are common to alkyl bromides. On the other hand, 2-bromopropene-1,  $\text{CH}_2=\text{CBr}-\text{CH}_3$ , a liquid boiling at  $48^\circ$ , is not hydrolyzed to the corresponding alcohol by treatment with alkali. It is difficult to remove a halogen from a carbon atom which is attached by two bonds to another carbon atom. However, vinyl bromide,  $\text{CH}_2=\text{CHBr}$  (b.p.  $16^\circ$ ), is converted into acetylene by either alcoholic or aqueous potash. It does not yield an ether when heated with an alcoholate. (See page 63 for the corresponding reaction of an alkyl halide.)

The group  $\text{CH}_2=\text{CH}-$  is known as the vinyl radical. Vinyl bromide is made by treating ethylene dibromide with an alcoholic solution of potassium hydroxide. Continued treatment with the same reagent results in the production of acetylene. Vinyl chloride (b.p.  $-18^\circ$ ) is made in the same way from ethylene dichloride. Vinyl alcohol is unknown (see the discussion of unsaturated alcohols on page 50).



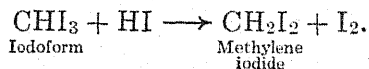
## ALKYL HALIDES

| ALKYL GROUP                    | FORMULA  | CHLORIDES     |                  | BROMIDES      |                  | IODIDES       |                  |
|--------------------------------|--|---------------|------------------|---------------|------------------|---------------|------------------|
|                                |  | Boiling Point | Specific Gravity | Boiling Point | Specific Gravity | Boiling Point | Specific Gravity |
| Methyl . . . . .               | $\text{CH}_3\text{X}$                                      | -23.7°        | 0.952 (0°)       | +4.6°         | 1.732 (0°)       | +42.6°        | 2.293 (18°)      |
| Ethyl . . . . .                | $\text{CH}_3\text{CH}_2\text{X}$                           | +12.2°        | 0.918 (8°)       | 38°           | 1.463 (13°)      | 72.3°         | 1.944 (14°)      |
| Normal propyl . . . . .        | $\text{CH}_3\text{CH}_2\text{CH}_2\text{X}$                | 46.5°         | 0.912 (0°)       | 71°           | 1.383 (0°)       | 102.5°        | 1.786 (0°)       |
| Isopropyl . . . . .            | $\text{CH}_3\text{CHXCH}_3$                                | 36.5°         | 0.882 (0°)       | 59.6°         | 1.340 (0°)       | 89.5°         | 1.774 (0°)       |
| Normal butyl . . . . .         | $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{X}$     | 78°           | 0.907 (0°)       | 101.6°        | 1.305 (0°)       | 127°          | 1.643 (0°)       |
| Isobutyl . . . . .             | $(\text{CH}_3)_2\text{CHCH}_2\text{X}$                     | 68.9°         | 0.895 (0°)       | 91.5°         | 1.264 (20°)      | 120.4°        | 1.640 (0°)       |
| Secondary butyl . . . . .      | $\text{CH}_3\text{CH}_2\text{CHXCH}_3$                     | 68°           | 0.871 (20°)      | 91.3°         | 1.251 (20°)      | 117.5°        | 1.626 (0°)       |
| Tertiary butyl . . . . .       | $(\text{CH}_3)_3\text{CX}$                                 | 51°           | 0.840 (20°)      | 73.3°         | 1.222 (20°)      | 100°          | 1.571 (0°)       |
| Normal amyl . . . . .          | $\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{X}$            | 105.7°        | 0.901 (0°)       | 127.9°        | 1.223 (20°)      | 156°          | 1.543 (0°)       |
| Isoamyl . . . . .              | $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{X}$          | 99.1°         | 0.893 (20°)      | 121°          | 1.215 (20°)      | 148°          | 1.540 (20°)      |
| Tertiary butylmethyl . . . . . | $(\text{CH}_3)_3\text{CCH}_2\text{X}$                      | —             | 0.879 (0°)       | —             | 1.235 (0°)       | —             | —                |
| Active amyl . . . . .          | $(\text{CH}_3)(\text{C}_2\text{H}_5)\text{CHCH}_2\text{X}$ | 99°           | 0.886 (17°)      | 120°          | 1.221 (20°)      | 148°          | 1.524 (20°)      |
| Normal hexyl . . . . .         | $\text{CH}_3(\text{CH}_2)_5\text{CH}_2\text{X}$            | 134°          | 0.872 (20°)      | 156°          | 1.173 (20°)      | 186°          | 1.443 (20°)      |
| Normal heptyl . . . . .        | $\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{X}$            | 159.5°        | 0.881 (16°)      | 179°          | 1.113 (16°)      | 203.8°        | 1.386 (16°)      |
| Normal octyl . . . . .         | $\text{CH}_3(\text{CH}_2)_7\text{CH}_2\text{X}$            | 184.6°        | 0.880 (16°)      | 201°          | 1.116 (16°)      | 225.5°        | 1.345 (16°)      |

*Ethyl chloride* is prepared in large quantities for use as a local anæsthetic. It is placed on the market in small glass tubes, each provided with a capillary opening, from which the liquid is sprayed upon the tissue to be frozen. The anæsthesia is produced, not by virtue of any chemical property of ethyl chloride, but merely by chilling caused by the rapid absorption of heat from the tissue by the very volatile liquid as it vaporizes.

*Methylene chloride*,  $\text{CH}_2\text{Cl}_2$ , is a liquid which boils at  $40^\circ$  and has a density of 1.337 g. per cubic centimeter. It is made from chloroform by reduction with zinc and hydrogen chloride in alcohol.

*Methylene iodide*,  $\text{CH}_2\text{I}_2$ , is obtained by reducing iodoform with hydrogen iodide and red phosphorus:



Phosphorus combines with the iodine and, in the presence of moisture, regenerates hydrogen iodide. Methylene iodide is a very heavy liquid (density = 3.292 g. per cubic centimeter at  $18^\circ$ ).

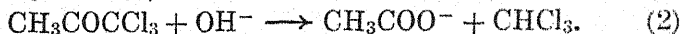
*Chloroform*,  $\text{CHCl}_3$  (m.p.  $-70^\circ$ , b.p.  $61^\circ$ ), is a heavy, colorless liquid possessing an agreeable odor and a sweet taste. It produces a burning sensation in the mouth. It is an excellent solvent for fats and many other types of compounds. It is still used extensively as an anæsthetic. Its effect upon the heart, however, renders its use dangerous in some cases.

Chloroform is prepared by distilling alcohol with a hypochlorite. Bleaching powder is a cheap source of hypochlorite ion and is commonly used. The alcohol is first oxidized to acetaldehyde,  $\text{CH}_3\text{CHO}$ , which in turn is converted into trichloroacetaldehyde,  $\text{CCl}_3\text{CHO}$ . Trichloroacetaldehyde (*chloral*) is hydrolyzed by a hot aqueous solution of any base, the products being chloroform and a salt of formic acid. It is assumed that the following reactions occur:



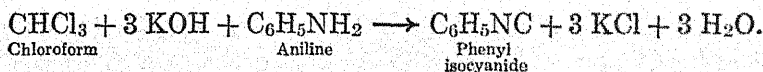
A bond between carbon atoms is not severed by hydrolysis except in cases of this type, where the two carbon atoms are bound to electronegative atoms.

Acetone may be substituted for alcohol as a source of chloroform, the by-product in this case being a salt of acetic acid :

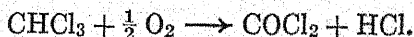


There is no positive proof that the above equations accurately represent the paths followed in the production of chloroform from alcohol and from acetone. Chloral,  $\text{CCl}_3\text{CHO}$ , a colorless, oily liquid, can be obtained from alcohol by treatment with free chlorine. In the absence of hydroxide ions it is not hydrolyzed to chloroform. Chloral combines with water, forming a hydrate,  $\text{CCl}_3\text{CH}(\text{OH})_2$ . This is a colorless crystalline solid which melts at  $57^\circ$ . When warmed with sulfuric acid the hydrate loses water, and free chloral is obtained by distillation.

In the presence of an alcoholic solution of a base, chloroform acts on primary amines, forming isocyanides or carbylamines. These compounds are characterized by disagreeable odors, detectable in extremely small quantities. The reaction affords a qualitative test for chloroform or for a primary amine :



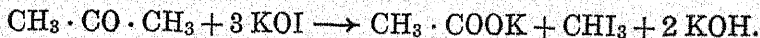
When exposed to light and air chloroform is slowly oxidized to phosgene and other products :



Vigorous oxidizing agents, such as chromic acid and perchloric acid, rapidly bring about the same change.

*Bromoform*,  $\text{CHBr}_3$  (m.p.  $7.8^\circ$ , b.p.  $150.4^\circ$ , sp. gr. 2.9), is made from acetone or alcohol through the action of bromine and a base.

*Iodoform*,  $\text{CHI}_3$  (m.p.  $119^\circ$ ), is prepared from alcohol by treatment with iodine and potassium carbonate. Potassium hypoiodite, formed by the action of the carbonate on iodine, is the active reagent. Acetone or any other ketone having the  $\text{CH}_3\text{CO}-$  group may be substituted for alcohol :

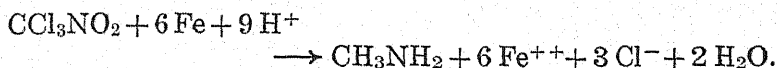


Iodoform crystallizes in yellow plates. It has a persistent odor, resembling that of saffron. It has antiseptic properties

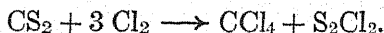
and is used as a germicide. It is soluble in alcohol and ether but insoluble in water.

Iodoform yields crystalline addition products with amines\* corresponding to the formulas  $\text{RNH}_2 \cdot \text{CHI}_3$ ,  $(\text{RNH}_2)_2\text{CHI}_3$ , and  $(\text{RNH}_2)_3\text{CHI}_3$ . Their formation is catalyzed by light.

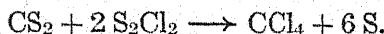
*Chloropicrin*, or nitrochloroform,  $\text{CCl}_3\text{NO}_2$ , a colorless liquid (b.p.  $112^\circ$ , sp. gr. 1.692 at  $0^\circ$ ), is prepared from chloral and nitric acid. Its vapor attacks the mucous membrane of the eye, and it has been used as a lachrymator in gas warfare. It explodes when heated. It is reduced by iron and acetic acid to methylamine:



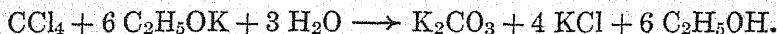
*Carbon tetrachloride*,  $\text{CCl}_4$ , is made from carbon disulfide by treatment with chlorine:



The sulfur chloride is removed by shaking the mixed products with a solution of sodium hydroxide, or it may be used as a source of chlorine by boiling it with an excess of carbon disulfide. Sulfur is precipitated, and an additional yield of carbon tetrachloride is obtained:



Carbon tetrachloride may be made also by passing chlorine gas into hot chloroform. It is decomposed by hot alcoholic potash:



It is used as a solvent and as a fire extinguisher.

*Ethylene chloride*,  $\text{CH}_2\text{Cl} \cdot \text{CH}_2\text{Cl}$ , is prepared by the action of chlorine on ethylene. Ethylene gas is passed into a warm mixture of manganese dioxide, sodium chloride, and 60 per cent sulfuric acid.

*Ethylene bromide*,  $\text{CH}_2\text{Br} \cdot \text{CH}_2\text{Br}$  (m.p.  $10^\circ$ ), is usually prepared by passing ethylene into bromine under water. The action is catalyzed by sunlight. The product is a colorless, oily liquid almost insoluble in water.

\* Dehn and Conner, *J. Am. Chem. Soc.*, 34, 1409 (1912).

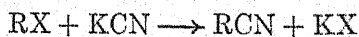
*Ethylene iodide*,  $\text{CH}_2\text{I} \cdot \text{CH}_2\text{I}$  (m.p.  $82^\circ$ ), is made by the action of ethylene on a paste of iodine in alcohol.

## PARAFFIN POLYHALIDES

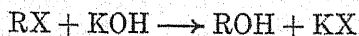
| CHLORIDES               |   |               | BROMIDES  |               |
|-------------------------|---|---------------|---|---------------|
| Name                    | Formula   | Boiling Point | Formula   | Boiling Point |
| Methylene chloride .    | $\text{CH}_2\text{Cl}_2$  | $+40.1^\circ$ | $\text{CH}_2\text{Br}_2$  | $+97.8^\circ$ |
| Chloroform . . . .      | $\text{CHCl}_3$   | $61.2^\circ$  | $\text{CHBr}_3$   | $130.4^\circ$ |
| Tetrachloromethane .    | $\text{CCl}_4$  | $76.8^\circ$  | $\text{CBr}_4$  | $189.5^\circ$ |
| Ethylidene chloride .   | $\text{CH}_3 \cdot \text{CHCl}_2$                                   | $57.3^\circ$  | $\text{CH}_3 \cdot \text{CHBr}_2$                                   | $110^\circ$   |
| Ethylene dichloride .   | $\text{CH}_2\text{Cl} \cdot \text{CH}_2\text{Cl}$                   | $83.7^\circ$  | $\text{CH}_2\text{Br} \cdot \text{CH}_2\text{Br}$                   | $131.7^\circ$ |
| Vinyl trichloride . .   | $\text{CH}_2\text{Cl} \cdot \text{CHCl}_2$                          | $113.5^\circ$ | $\text{CH}_2\text{Br} \cdot \text{CHBr}_2$                          | $188.4^\circ$ |
| Methyl chloroform . .   | $\text{CH}_3 \cdot \text{CCl}_3$                                    | $74.1^\circ$  | $\text{CH}_3 \cdot \text{CBr}_3$                                    | —             |
| Acetylene tetrachloride | $\text{CHCl}_2 \cdot \text{CHCl}_2$                                 | $146.3^\circ$ | $\text{CHBr}_2 \cdot \text{CHBr}_2$                                 | $114^\circ *$ |
| Pentachloroethane . .   | $\text{CHCl}_2 \cdot \text{CCl}_3$                                  | $162^\circ$   | $\text{CHBr}_2 \cdot \text{CBr}_3$                                  | $103^\circ *$ |
| Hexachloroethane . .    | $\text{CCl}_3 \cdot \text{CCl}_3$                                   | $185^\circ$   | $\text{CBr}_3 \cdot \text{CBr}_3$                                   | $210^\circ$   |
| Propylidene chloride .  | $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CHCl}_2$                 | $87^\circ$    | $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CHBr}_2$                 | $130^\circ$   |
| 1, 2-Dichloropropane .  | $\text{CH}_3 \cdot \text{CHCl} \cdot \text{CH}_2\text{Cl}$          | $96.8^\circ$  | $\text{CH}_3 \cdot \text{CHBr} \cdot \text{CH}_2\text{Br}$          | $140^\circ$   |
| Trimethylene chloride   | $\text{CH}_2\text{Cl} \cdot \text{CH}_2 \cdot \text{CH}_2\text{Cl}$ | $125^\circ$   | $\text{CH}_2\text{Br} \cdot \text{CH}_2 \cdot \text{CH}_2\text{Br}$ | $167^\circ$   |

The alkyl halides are used as sources of many types of organic compounds. We have already considered their uses in the preparation of hydrocarbons and alcohols. Some of the types of compounds that may be made from alkyl halides are indicated below:

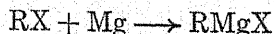
Alkyl cyanides:



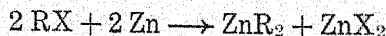
Alcohols:



Magnesium alkyl halides:



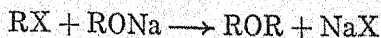
Zinc alkyls:



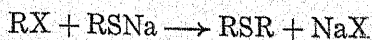
Mercaptans:



Ethers:

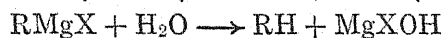
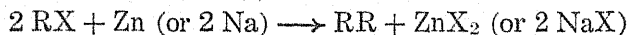
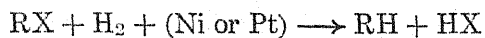


Thioethers:

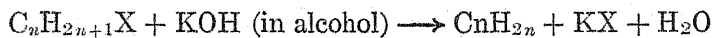


\* At 13 mm. Hg pressure.

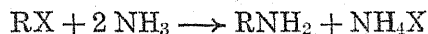
Hydrocarbons (saturated):



Hydrocarbons (unsaturated):



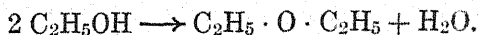
Amines:



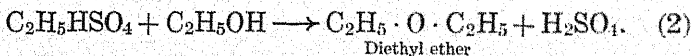
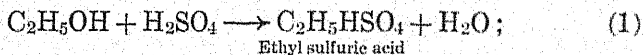
Many of these reactions will be considered in detail later.

## ETHERS

The aliphatic ethers are alkyl oxides corresponding to the general formula  $R \cdot O \cdot R'$ . The two alkyl radicals may be alike or different. The ethers of low molecular weight are derived from alcohols through the elimination of one molecule of water from two molecules of alcohol. Thus, from methyl alcohol we obtain dimethyl ether and from ethyl alcohol diethyl ether:



**Preparation.** 1. The formation of an ether from an alcohol by treatment with sulfuric acid is accomplished in two stages. In the first step sulfuric acid combines with the alcohol, forming an alkyl sulfuric acid, and in the second step this intermediate product reacts with more alcohol, forming an ether and regenerating sulfuric acid. Thus, in the preparation of ordinary ether from ethyl alcohol, we have

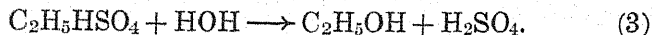


In the practical procedure the alcohol and acid are mixed in molecular proportions and heated in a distilling flask to  $140^\circ$ . More alcohol is then allowed to flow into the mixture as rapidly as ether distills out.

Only ethers of low molecular weight can be made in this manner, for the alcohols having more than three carbon atoms all react with sulfuric acid to form unsaturated hydrocarbons. At higher temperatures the alcohols of low molecular weight also yield unsaturated hydrocarbons. At  $165^\circ$  ethyl sulfuric acid is decomposed, with the production of ethylene; hence it is important to control the temperature in the manufacture of ether.

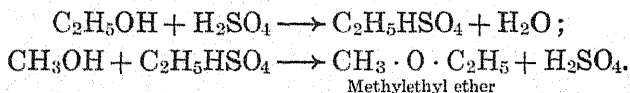


The sulfuric acid used in equation (1) is regenerated in the second step, (2), and the process can be carried on without interruption until approximately fifteen times as much alcohol as represented in equation (1) has been used. The reaction finally stops on account of dilution with the water formed. Sulfur dioxide and other by-products are formed in small amounts, owing to oxidation of some of the alcohol by the hot sulfuric acid. Ethyl sulfuric acid reacts with water as follows :



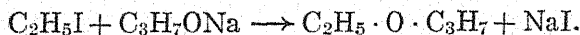
This is a reversal of equation (1). The velocity of reaction (3) increases as the concentration of water in the mixture increases. It gradually approaches the velocity of the reverse process (1), and finally a practical limit is reached beyond which it is not economical to force the reaction by further additions of alcohol.

A mixed ether (that is, one containing two different alkyl radicals) can be made by forming the alkyl sulfuric acid with one alcohol and mixing the product with another alcohol before distilling :



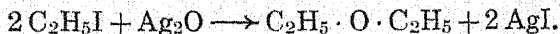
The process, however, yields more than one ether. In this case dimethyl ether and diethyl ether are contaminating by-products of the reaction.

2. An ether is formed when a mixture of an alkyl halide and an alcoholate is distilled :



This is the most satisfactory method for making ethers of high molecular weight.

3. Ethers have been made by heating alkyl halides with silver oxide :



This method has no practical value.

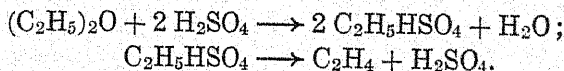
4. Phosphoric acid may be substituted for sulfuric acid in the preparation of an ether from an alcohol of low molecular weight.

## ETHERS

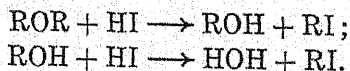
| NAME                                     | FORMULA  | BOILING POINT | SPECIFIC GRAVITY     |
|--|--|---------------|----------------------|
| Dimethyl ether . . . . .                 | $\text{CH}_3 \cdot \text{O} \cdot \text{CH}_3$                         | $-24.9^\circ$ | —                    |
| Methylethyl ether . . . . .              | $\text{CH}_3 \cdot \text{O} \cdot \text{C}_2\text{H}_5$                | $+7.9^\circ$  | 0.725 ( $0^\circ$ )  |
| Diethyl ether . . . . .                  | $\text{C}_2\text{H}_5 \cdot \text{O} \cdot \text{C}_2\text{H}_5$       | $34.6^\circ$  | 0.714 ( $20^\circ$ ) |
| Methyl- <i>n</i> -propyl ether . . . . . | $\text{CH}_3 \cdot \text{O} \cdot \text{C}_3\text{H}_7$                | $38.9^\circ$  | 0.747 ( $0^\circ$ )  |
| Methyl- <i>isopropyl</i> ether . . . . . | $\text{CH}_3 \cdot \text{O} \cdot \text{C}_3\text{H}_7$                | $32.5^\circ$  | 0.735 ( $20^\circ$ ) |
| Ethyl- <i>n</i> -propyl ether . . . . .  | $\text{C}_2\text{H}_5 \cdot \text{O} \cdot \text{C}_3\text{H}_7$       | $61.4^\circ$  | 0.732 ( $20^\circ$ ) |
| Ethyl- <i>isopropyl</i> ether . . . . .  | $\text{C}_2\text{H}_5 \cdot \text{O} \cdot \text{C}_3\text{H}_7$       | $54^\circ$    | 0.745 ( $0^\circ$ )  |
| Dipropyl ether . . . . .                 | $\text{C}_3\text{H}_7 \cdot \text{O} \cdot \text{C}_3\text{H}_7$       | $89^\circ$    | 0.763 ( $0^\circ$ )  |
| Di- <i>isopropyl</i> ether . . . . .     | $\text{C}_3\text{H}_7 \cdot \text{O} \cdot \text{C}_3\text{H}_7$       | $69^\circ$    | 0.743 ( $0^\circ$ )  |
| Ethyl- <i>n</i> -butyl ether . . . . .   | $\text{C}_2\text{H}_5 \cdot \text{O} \cdot \text{C}_4\text{H}_9$       | $91.4^\circ$  | 0.769 ( $0^\circ$ )  |
| Ethyl- <i>isobutyl</i> ether . . . . .   | $\text{C}_2\text{H}_5 \cdot \text{O} \cdot \text{C}_4\text{H}_9$       | $80^\circ$    | 0.751 ( $20^\circ$ ) |
| Ethyl tertiary butyl ether . . . . .     | $\text{C}_2\text{H}_5 \cdot \text{O} \cdot \text{C}_4\text{H}_9$       | $141^\circ$   | 0.784 ( $0^\circ$ )  |
| Di- <i>n</i> -butyl ether . . . . .      | $\text{C}_4\text{H}_9 \cdot \text{O} \cdot \text{C}_4\text{H}_9$       | $140.9^\circ$ | 0.769 ( $20^\circ$ ) |
| Di- <i>isobutyl</i> ether . . . . .      | $\text{C}_4\text{H}_9 \cdot \text{O} \cdot \text{C}_4\text{H}_9$       | $122.5^\circ$ | 0.762 ( $20^\circ$ ) |
| Di- <i>isocamyl</i> ether . . . . .      | $\text{C}_5\text{H}_{11} \cdot \text{O} \cdot \text{C}_5\text{H}_{11}$ | $172.2^\circ$ | 0.781 ( $15^\circ$ ) |

**Properties.** With the exception of the first two members, the ethers included in this table are colorless liquids. Some higher members of the series are solids. They are all lighter than water and very slightly soluble in water. They are soluble in alcohols, hydrocarbons, chloroform, and other organic liquids. There are very few general reactions of the ethers, for they are inert compounds. They are not attacked by alkalies nor by the free alkali metals. They are unaffected by cold phosphorus pentachloride, dilute acids, and mild oxidizing and reducing agents.

Hot concentrated nitric acid or chromic acid converts an ether into the same oxidation products that would be obtained from the corresponding alcohol. Prolonged heating with concentrated sulfuric acid converts diethyl ether into ethyl sulfuric acid, with the ultimate production of ethylene:



The decomposition of an ether is much more readily accomplished through the action of hot hydrogen iodide:

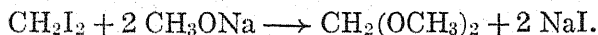


*Ethyl ether.* Diethyl ether is the most important representative of the group. It is manufactured from alcohol and

sulfuric acid in large quantities for use as an anæsthetic and as a solvent for organic compounds. It is freed from sulfur dioxide by washing it with an aqueous alkaline solution. The commercial product usually contains small quantities of alcohol and water. When pure ether is required, the washed ether is shaken with granular calcium chloride to remove most of the water and alcohol and then allowed to stand in contact with sodium wire as long as hydrogen is evolved. It is then distilled under anhydrous conditions.

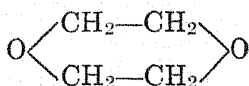
Ethyl ether is a light, colorless, mobile liquid. It dissolves in 11.1 times its own volume of water at 25°. Ether at the same temperature dissolves 2 per cent of its own volume of water. On account of its high vapor pressure at ordinary temperatures and the fact that its vapor forms an explosive mixture with air, ether must be kept away from flames.

*Methylal* (methylene dimethyl ether or dimethoxymethane),  $\text{CH}_3 \cdot \text{O} \cdot \text{CH}_2 \cdot \text{O} \cdot \text{CH}_3$ , is made by the action of sodium methylate on methylene iodide:



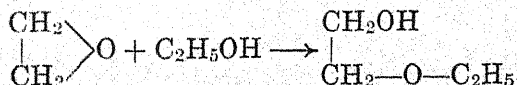
It is a colorless liquid having a pleasant odor. It boils at 44° and solidifies at -105°. Methylal is miscible with alcohol and ether in all proportions, and it is very soluble in water.

*Dioxane*. Dioxane (1, 4-dioxane) is made by heating ethylene glycol with sulfuric acid or with zinc chloride. The compound corresponds to the following structural formula:



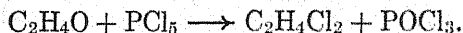
It is a colorless liquid which boils at 101.5° and freezes at 11.7°. It is a good solvent for many classes of compounds, including the cellulose esters that are used in the manufacture of lacquers and artificial silk. Dioxane can be freed from water by treatment with lime or metallic sodium.

*Cellosolves*. Products formed from ethylene oxide and alcohols are sold under the trade name of cellosolve. The reaction between ethyl alcohol and ethylene oxide proceeds as follows:



## ALDEHYDES AND KETONES

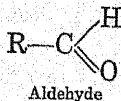
Primary alcohols are converted by oxidation into aldehydes without loss of carbon. The aldehyde molecule differs in composition from the corresponding alcohol by two hydrogen atoms. The properties of alcohols that depend upon the hydroxyl group are lacking in aldehydes. They contain no hydrogen that is replaceable by metals. Phosphorus pentachloride acts upon the aldehyde molecule, replacing oxygen only, and for each atom of oxygen removed two atoms of chlorine are introduced:



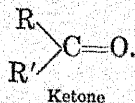
Evidently the hydroxyl hydrogen of the alcohol is one of the two atoms removed by oxidation. The  $-\text{CH}_2\text{OH}$  group of

the alcohol is thus converted into  $-\text{C} \begin{smallmatrix} \text{H} \\ \diagup \\ \text{O} \end{smallmatrix}$ . In a similar man-

ner ketones are formed from secondary alcohols; the group  $-\text{CHOH}-$  is converted into  $-\text{CO}-$ . Aldehydes and ketones have in common the group  $\text{>C=O}$ , known as the carbonyl group. In ketones two valence bonds of the carbonyl group are attached to carbon radicals. In aldehydes one bond is attached to hydrogen, and (except in the case of formaldehyde) the other is held by a carbon radical. The general formulas are



and



**Nomenclature.** The aldehydes are named from the acids which they produce when oxidized. Formaldehyde, or formic aldehyde,  $\text{H} \cdot \text{CHO}$ , is the member of the series from which formic acid may be derived. Acetaldehyde, or acetic aldehyde,  $\text{CH}_3 \cdot \text{CHO}$ , yields acetic acid when oxidized.

Ketones are named from the radicals attached to the carbonyl group. Thus  $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_3$  is dimethyl ketone, and  $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}(\text{CH}_3)_2$  is methylisopropyl ketone.

According to the Geneva system an aldehyde is named from the hydrocarbon that has the same number of carbon atoms in the longest continuous chain. The final *e* of the hydrocarbon name is changed to *al* to indicate the presence of the aldehyde group. Thus  $\text{H} \cdot \text{CHO}$  is methanal,  $\text{CH}_3 \cdot \text{CHO}$  is ethanal, and so on. A ketone is named by changing the final *e* of the name of the corresponding hydrocarbon to *one*. A number following the suffix *one*, or immediately preceding the name containing this suffix, indicates the position of the carbonyl group; for example,  $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_3$  is pentanone-3 or 3-pentanone, and  $(\text{CH}_3)_2\text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{CH}_3$  is 5-methyl-hexanone-2 or 5-methyl-2-hexanone.

## ALDEHYDES

| NAME                            | FORMULA                                | MELTING POINT  | BOILING POINT | SPECIFIC GRAVITY      |
|---------------------------------|--|----------------|---------------|-----------------------|
| Formaldehyde . . . . .          | $\text{HCHO}$                          | $-92^\circ$    | $-21^\circ$   | 0.815 ( $-20^\circ$ ) |
| Acetaldehyde . . . . .          | $\text{CH}_3\text{CHO}$                | $-123.5^\circ$ | $+20.2^\circ$ | 0.781 ( $20^\circ$ )  |
| Propionaldehyde . . . . .       | $\text{C}_2\text{H}_5\text{CHO}$       | $-81^\circ$    | $48.8^\circ$  | 0.807 ( $20^\circ$ )  |
| Normal butyraldehyde . . . . .  | $\text{C}_3\text{H}_7\text{CHO}$       | $-99^\circ$    | $75.7^\circ$  | 0.817 ( $20^\circ$ )  |
| Isobutyraldehyde . . . . .      | $\text{C}_3\text{H}_7\text{CHO}$       | $-65.9^\circ$  | $61^\circ$    | 0.794 ( $20^\circ$ )  |
| Normal valeraldehyde . . . . .  | $\text{C}_4\text{H}_9\text{CHO}$       | —              | $103.4^\circ$ | 0.819 ( $11^\circ$ )  |
| Isovaleraldehyde . . . . .      | $\text{C}_4\text{H}_9\text{CHO}$       | $-51^\circ$    | $92.5^\circ$  | 0.798 ( $20^\circ$ )  |
| Trimethylacetaldehyde . . . . . | $\text{C}_4\text{H}_9\text{CHO}$       | $+3^\circ$     | $75^\circ$    | 0.793 ( $20^\circ$ )  |
| Undecanaldehyde . . . . .       | $\text{C}_{10}\text{H}_{21}\text{CHO}$ | $-4^\circ$     | $117^\circ$ * | 0.825 ( $23^\circ$ )  |

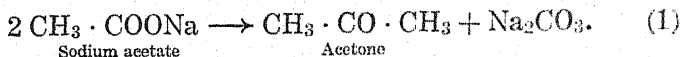
## KETONES

| NAME                          | FORMULA  | MELTING POINT | BOILING POINT | SPECIFIC GRAVITY     |
|-------------------------------|--|---------------|---------------|----------------------|
| Acetone . . . . .             | $\text{CH}_3\text{COCH}_3$                         | $-94.3^\circ$ | $+56.1^\circ$ | 0.791 ( $20^\circ$ ) |
| Methylethyl ketone . . . . .  | $\text{CH}_3\text{COC}_2\text{H}_5$                | $-86.4^\circ$ | $79.6^\circ$  | 0.805 ( $20^\circ$ ) |
| Diethyl ketone . . . . .      | $\text{C}_2\text{H}_5\text{COC}_2\text{H}_5$       | $-42^\circ$   | $101.7^\circ$ | 0.821 ( $15^\circ$ ) |
| Methylpropyl ketone . . . . . | $\text{CH}_3\text{COC}_3\text{H}_7$                | $-77.3^\circ$ | $101.8^\circ$ | 0.808 ( $20^\circ$ ) |
| Dipropyl ketone . . . . .     | $\text{C}_3\text{H}_7\text{COC}_3\text{H}_7$       | $-32.6^\circ$ | $143.5^\circ$ | 0.820 ( $20^\circ$ ) |
| Di-isopropyl ketone . . . . . | $\text{C}_3\text{H}_7\text{COC}_3\text{H}_7$       | —             | $123.7^\circ$ | 0.806 ( $20^\circ$ ) |
| Dipentyl ketone . . . . .     | $\text{C}_5\text{H}_{11}\text{COC}_5\text{H}_{11}$ | $+14.6^\circ$ | $226.3^\circ$ | 0.826 ( $20^\circ$ ) |
| Diethyl ketone . . . . .      | $\text{C}_6\text{H}_{13}\text{COC}_6\text{H}_{13}$ | $+30.5^\circ$ | $264^\circ$   | 0.825 ( $30^\circ$ ) |
| Methylhexyl ketone . . . . .  | $\text{CH}_3\text{COC}_6\text{H}_{13}$             | $-21.6^\circ$ | $172.7^\circ$ | 0.820 ( $16^\circ$ ) |
| Methyloctyl ketone . . . . .  | $\text{CH}_3\text{COC}_8\text{H}_{17}$             | $+3.5^\circ$  | $211^\circ$   | 0.825 ( $20^\circ$ ) |

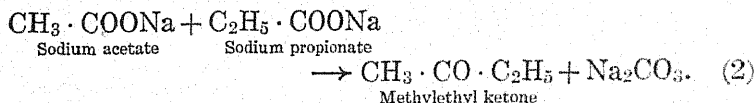
\* At 18 mm. pressure.

**Preparation.** Aldehydes and ketones may be prepared by the following methods:

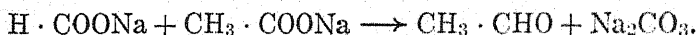
1. Dry distillation of a salt of an organic acid results in the formation of a ketone:



Methylethyl ketone is made by distilling a mixture of sodium acetate and sodium propionate:

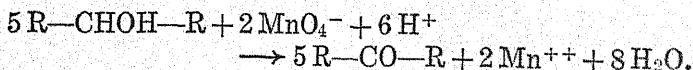
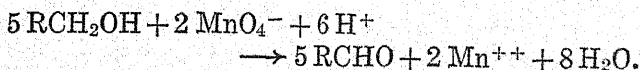
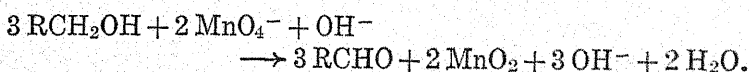


Mixed products are obtained from reactions of mixed salts, for a ketone may be formed from any two salt molecules. In addition to methylethyl ketone, formed as indicated in equation (2), the same mixture of salts yields dimethyl ketone and diethyl ketone. A mixture of a formate with a salt of another organic acid may be distilled to produce an aldehyde:



Formaldehyde and acetone are by-products in this reaction.

2. Alcohols are oxidized by dichromate ion in acid solution or by an acid or alkaline solution of permanganate ion. A primary alcohol yields an aldehyde; a secondary alcohol yields a ketone:

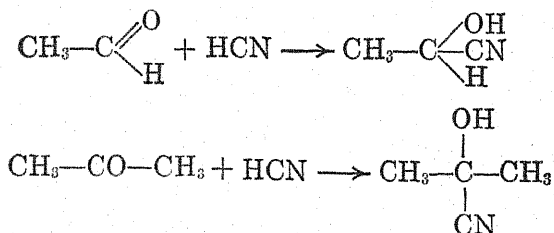


The reactions of aldehydes and ketones depend upon the activity of the carbonyl group. Acetaldehyde,  $\text{CH}_3 \cdot \text{CHO}$ , and acetone,  $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_3$ , are typical representatives of the two classes, and the formulas of these compounds are used in the following equations, which represent general reactions.

**Addition reactions.** Many reagents form addition products with aldehydes and ketones by breaking the double bond between carbon and oxygen in the carbonyl group. The negative

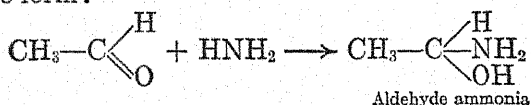
radical of the reagent attaches to the carbon atom, and the positive atom or group combines with the oxygen.

*Hydrocyanic acid.* A cyanhydrin is formed by the direct addition of hydrogen cyanide to an aldehyde or ketone:

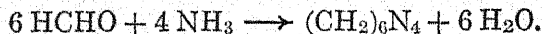


A cyanhydrin is a compound in which there is a cyanide radical and a hydroxyl group attached to the same carbon atom. This reaction is important, for it affords a means of introducing a new carbon atom into the molecule. The addition product may be used in the synthesis of other classes of compounds. The  $-\text{CN}$  group is easily hydrolyzed to  $-\text{COOH}$ , giving rise to an acid, or it may be reduced to  $-\text{CH}_2\text{NH}_2$ , yielding an amine.

*Ammonia.* Ammonia combines with aldehydes, forming addition products analogous to the compounds formed by addition of hydrocyanic acid. The procedure in the case of volatile aldehydes is to pass the vapor, mixed with ammonia gas, into cold ether. The aldehyde ammonia is precipitated in crystalline form:



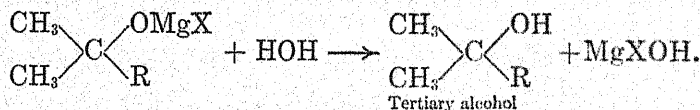
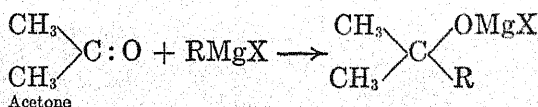
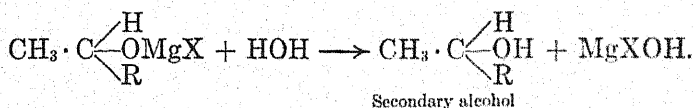
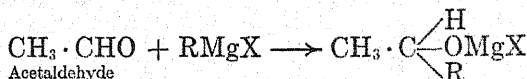
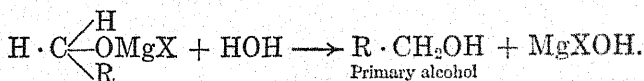
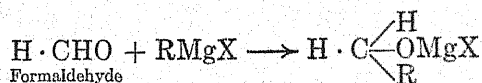
Aldehyde ammonias, like the free aldehydes, have a tendency to polymerize. Acetaldehyde ammonia, as ordinarily prepared, has the formula  $(\text{CH}_3\text{CHOHNH}_2)_3$ . These compounds are decomposed by acids, the aldehydes being regenerated. Ketones fail to form addition products with ammonia. Formaldehyde is exceptional in its behavior with ammonia. It forms a basic substance known as hexamethylenetetramine:



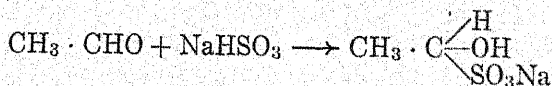
*The Grignard reagent.* Magnesium dissolves in an ether solution of an alkyl halide, forming an alkyl magnesium compound,



$\text{RMgX}$ , commonly called the Grignard reagent (see the section on the Grignard Reaction, p. 395). Alkyl magnesium halides form, with aldehydes and ketones, addition products which may be hydrolyzed to produce alcohols. In this way formaldehyde may be used in the preparation of a primary alcohol. Any other aldehyde gives rise to a secondary alcohol, and ketones are converted into tertiary alcohols:



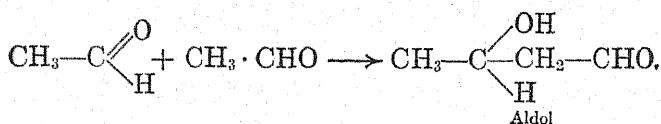
*Bisulfites.* Sodium hydrogen sulfite forms a crystalline addition product with all aldehydes and with ketones in which a methyl radical is attached to the  $-\text{CO}-$  group:



The aldehyde may be regenerated by distilling the solid addition product with sodium carbonate or by heating it with an acid.\*

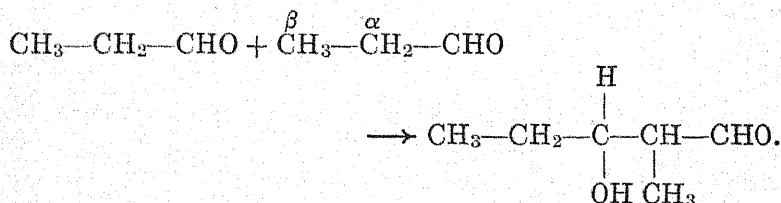
\* For discussions concerning the structure of the bisulfite addition product: see G. Schroeter, *Ber.*, 61 B, 1616 (1928), and F. Raschig and W. Prah, *Ann.*, 448, 265 (1926).

*Aldol condensation.\** In the presence of sodium ethylate, sodium acetate, potassium carbonate, or hydrogen chloride, acetaldehyde condenses to form a compound having twice the molecular weight of the original aldehyde. The compound consists of two aldehyde molecules, chemically combined, and is known as aldol. The reaction involved is similar to the addition of HCN or NaHSO<sub>4</sub>. Hydrogen attaches to the carbonyl oxygen, and the residue of the molecule becomes attached to carbon:



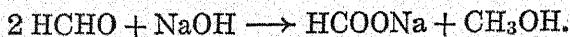
Similar condensations of other aldehydes have been induced. Invariably it is hydrogen on the  $\alpha$ -carbon atom (that is, on the carbon atom adjacent to the —CHO group) which takes part in the reaction.

Propionaldehyde, under the influence of dilute alkali, condenses as follows:



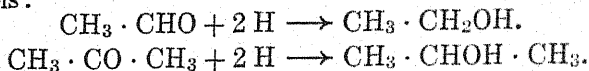
Aldehydes having no hydrogen attached to the  $\alpha$ -carbon do not undergo the aldol condensation.

When an aldehyde is treated with a concentrated solution of an alkali, condensation does not stop with the production of an aldol. Colored resinous substances of unknown structures are formed. Formaldehyde, however, does not resinify when warmed with a concentrated solution of a base. Under this treatment half of the formaldehyde molecules are oxidized to formic acid and half are reduced to methyl alcohol:

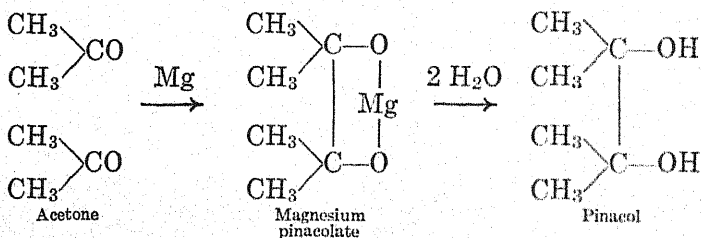


\* Condensation is a term applied to a variety of reactions in which two or more molecules, alike or different, unite by the linking of carbon atoms, with or without the elimination of water.

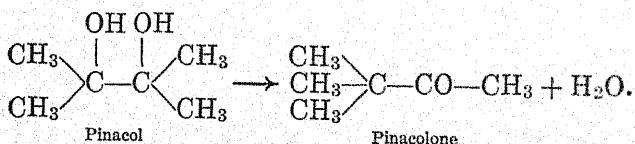
**Reduction.** Sodium amalgam or any source of active hydrogen reduces aldehydes and ketones with the formation of alcohols:



Ditertiary alcohols, pinacols, are formed also in the reduction of ketones. The secondary alcohol is the chief product when an aqueous or an alcoholic solution of the ketone is reduced by sodium amalgam. A good yield of tetramethyl glycol (pinacol) is obtained from acetone by treatment with mercuric chloride and magnesium turnings in dry benzene. Magnesium pinacolate produced in this way is hydrolyzed by subsequent treatment with water. Pinacol and magnesium hydroxide are the hydrolysis products.



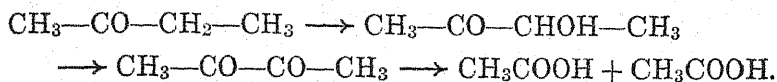
When warmed with sulfuric acid, the pinacol undergoes an intramolecular rearrangement in which it loses a molecule of water and forms pinacolone, or tertiary butyl-methyl ketone:



The mechanism of this rearrangement is discussed in a later chapter (see page 441).

**Oxidation.** On oxidation aldehydes yield acids without loss of carbon, but ketones yield either carbon dioxide and water or acids containing fewer carbon atoms than in the original ketone; the products formed depend upon the nature of the ketone, the vigor of the oxidizing agent, the temperature, the concentration, the solvent used, and other factors. The first oxidation products of ketones are acids formed by breaking the molecule at the position of the carbonyl group. The posi-

tion in a molecule where oxidation has already occurred is the most susceptible to further oxidation. On this account a secondary alcohol is oxidized to a ketone. The  $\text{—CHOH—}$  group is converted to  $\text{—CO—}$  before any other part of the molecule is attacked. In the ketone an atom adjacent to the  $\text{>CO}$  group is in the position most susceptible to oxidation. The oxidation of the compound  $\text{CH}_3\text{—CO—CH}_2\text{—CH}_3$  probably takes the following course :



The ketone  $\text{CH}_3\text{—CH}_2\text{—CO—CH}_2\text{—CH}$   $\begin{smallmatrix} \text{CH}_3 \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{CH}_3 \end{smallmatrix}$  yields four acids, namely,  $\text{CH}_3\text{CH}_2\text{COOH}$ ,  $\begin{smallmatrix} \text{CH}_3 \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{CH}_3 \end{smallmatrix} \text{CHCOOH}$ ,  $\text{CH}_3\text{COOH}$ , and  $\begin{smallmatrix} \text{CH}_3 \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{CH}_3 \end{smallmatrix} \text{CHCH}_2\text{COOH}$ . These products indicate that in

every case the ketone molecule breaks between the carbonyl group and an adjacent carbon atom; but not always on the same side of the  $\text{—CO—}$  group. The four acids are not produced in equal amounts. The reaction which leaves the carbonyl group attached to the smaller of the two radicals predominates.

*Fehling's solution.\** Aliphatic aldehydes and a few ketones† are oxidized by an alkaline solution of cupric sulfate. Fehling's solution is made by adding copper sulfate to a solution of sodium potassium tartrate and sodium hydroxide. In the presence of tartrates cupric hydroxide is not precipitated. A clear, dark blue solution is formed which, when warmed with an aldehyde,

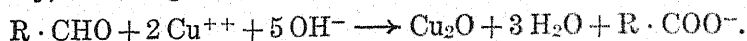
\* In Fehling's solution the copper is present chiefly in the anion of the complex salt



A small amount of cupric ion,  $\text{Cu}^{++}$ , is present also, and since all forms of copper in the mixture are in equilibrium with each other, the oxidizing effect of the reagent can be represented by using, in the equation, either the cupric ion or the complex copper tartrate ion.

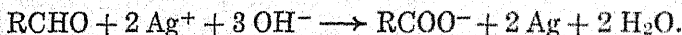
† Fructose reduces Fehling's solution (see page 157). Ketones having the group  $\text{—CHOH—CO—}$  are very easily oxidized.

yields a brick-red precipitate of cuprous oxide. In a qualitative way, the change may be represented by the equation



This reaction is of clinical value. It is the test ordinarily applied to determine the presence or absence of glucose in the urine. There is a definite relationship between the amount of cuprous oxide precipitated and the amount of sugar oxidized (a relationship not accurately represented by the above equation), so that the reaction forms the basis of quantitative methods for estimating the sugar present in the urine — a matter of prime importance in the diagnosis and treatment of diabetes.

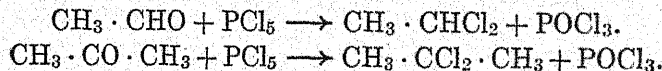
*Tollen's reagent.\** An ammoniacal solution of silver oxide may be made by precipitating silver oxide from silver nitrate solution by the addition of sodium hydroxide and redissolving the precipitate in dilute ammonium hydroxide. A solution prepared in this way is called Tollen's reagent. When it is warmed with an aldehyde in a test tube or beaker, a fine mirror is produced on the walls of the container through the plating out of metallic silver:



A few ketones reduce silver oxide, but by placing a time limit upon the reaction the test may be used to distinguish aldehydes from ketones. Aldehydes are oxidized rapidly by this reagent.

*Other reactions.* There are other reagents that react with aldehydes and ketones, with results that do not fall within the categories listed above.

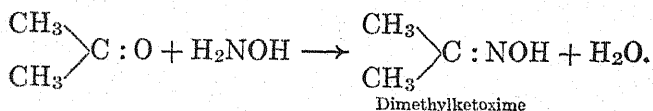
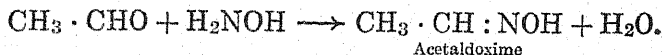
*Phosphorus pentachloride* acts upon aldehydes and ketones, replacing the carbonyl oxygen by two chlorine atoms:



*Hydroxylamine.†* Aldehydes and ketones combine with hydroxylamine, eliminating water and forming oximes:

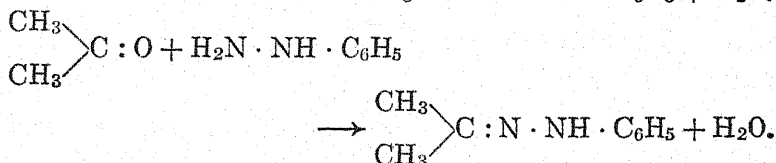
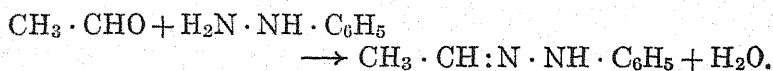
\* In Tollen's reagent the silver is present in the form of a complex ion corresponding to the formula  $Ag^{+}(NH_3)_2$ .

† Hydroxylamine,  $NH_2OH$ , a white solid (m.p.  $33^{\circ}$ , b.p.  $58^{\circ}$  under 22 mm. pressure), is an unstable compound. It decomposes rapidly, even below its melting point, and it explodes if heated to  $130^{\circ}$ . It forms stable salts with acids. The hydrochloride,  $NH_2OH \cdot HCl$ , is generally used in the reactions listed above. A



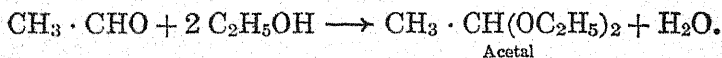
The oximes are readily changed by intramolecular rearrangement into totally different compounds. The change is discussed under the Beckmann Rearrangement.

*Phenylhydrazine.* With aldehydes and ketones, phenylhydrazine\* forms compounds known as hydrazones:



Hydrazones are hydrolyzed by boiling them with acids, the original aldehyde or ketone being regenerated.

*Alcohols.* When aldehyde and alcohol mixtures are saturated with hydrogen chloride gas, acetals are formed. A few ketones react with alcohols in the same way.

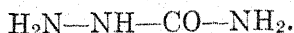


The lower members of the series of acetals are volatile liquids of aromatic odor. They are less dense than water and quite stable. They dissolve in alcohol and in ether; but are almost insoluble in water. When digested for a long time with dilute hydrochloric acid at 100°, they are hydrolyzed, the aldehydes and alcohols being regenerated. They are not hydrolyzed in alkaline solution.

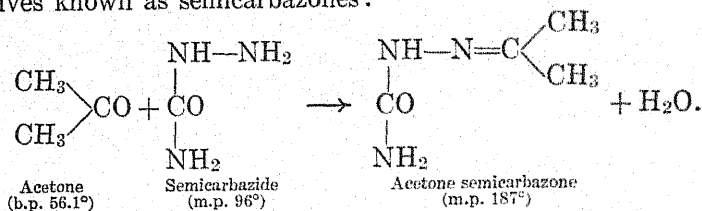
stronger base than hydroxylamine is added to remove hydrochloric acid from the salt and liberate free hydroxylamine in the presence of the aldehyde or ketone. Hydroxylamine hydrochloride is made by the action of tin on a mixture of dilute nitric and hydrochloric acid solutions. Nitric acid is reduced by hydrogen liberated from hydrochloric acid. The tin ions are removed from the solution by precipitation with hydrogen sulfide. The stannous sulfide is filtered out, and the filtrate is evaporated to dryness. From the residue hydroxylamine hydrochloride is extracted with absolute alcohol.

\* For a description of phenylhydrazine,  $\text{C}_6\text{H}_5\text{NHNH}_2$ , and its salts see page 229.

*Semicarbazide.* A crystalline derivative of hydrazine, called semicarbazide, is made by heating a mixture of urea and hydrazine hydrate. It corresponds to the formula



It reacts readily with aldehydes and ketones, forming derivatives known as semicarbazones:



*Schiff's reagent.* Magenta, a beautiful red dye, is decolorized by sulfur dioxide. The color of this reagent is promptly restored by a few drops of an aldehyde solution.\*

### THE LOWER ALDEHYDES AND KETONES

*Formaldehyde*,  $\text{HCHO}$ , is a gas under ordinary conditions of temperature and pressure. It has an irritating effect upon the mucous membrane, causes suffocation, and produces tears. Most aldehydes resinify when warmed with concentrated alkalis, but the behavior of formaldehyde in alkaline solution is exceptional. Instead of forming a resin it undergoes oxidation and reduction, forming a salt of formic acid and methyl alcohol.

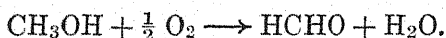
Formaldehyde is soluble in water and it is usually placed on the market in the form of an aqueous solution (formalin, 40 per cent  $\text{HCHO}$ ) or as "paraform," a waxlike solid polymer of formaldehyde. The tendency of formaldehyde to polymerize—that is, for two or more molecules to unite with each other—is so pronounced that evaporation of formalin on a steam bath results in the formation of a large amount of paraform,  $(\text{CH}_2\text{O})_n$ . This solid substance decomposes when heated, yielding formaldehyde gas. It is used in the manufacture of candles, which on burning release the gas in sufficient quantities to serve for fumigation. The pure gas liquefies at  $-21^\circ$ , and on standing the liquid polymerizes. It is possible to secure crystals of pure

\* For the composition of the colored product and the technique of applying the test see Porter, Stewart, and Branch's "Methods of Organic Chemistry" (Ginn and Company).



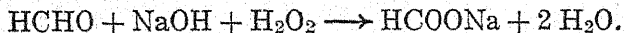
formaldehyde by rapidly cooling the liquid to  $-92^{\circ}$  by means of liquid air. The crystals are soluble in cold ether. The molecular weight of formaldehyde in the vapor phase corresponds to the formula  $\text{CH}_2\text{O}$ . In solution it varies with the concentration. In concentrated solutions the dissolved molecules associate, forming aggregates consisting of double or triple molecules. There is also evidence of hydration, the single, double, and triple molecules of the aldehyde uniting with the solvent to form heavier molecules. A crystalline polymer of definite composition and molecular weight has been isolated from the amorphous mass formed when formalin is evaporated. It is the chief product obtained when anhydrous liquid formaldehyde polymerizes. The compound is known as trioxymethylene. It sublimes unchanged and dissolves in water. It has the formula  $(\text{CH}_2\text{O})_3$ . A different type of condensation is induced by saturating an aqueous solution of formaldehyde with calcium hydroxide and allowing the mixture to stand for several days. The product formed is commonly called acrose. It corresponds to the formula  $\text{C}_6\text{H}_{12}\text{O}_6$  and has the properties of a sugar.

Formaldehyde is prepared commercially by passing a mixture of air and methyl alcohol vapor over hot copper:



Formaldehyde renders albuminous substances tough and insoluble and it is used in large quantities in the preparation of tissues for histological work. It is employed also in the manufacture of various types of plastics, including artificial ivory from casein and bakelite from phenol.

A quantitative estimation of formaldehyde may be made by oxidizing it with hydrogen peroxide in the presence of a measured excess of standard sodium hydroxide solution:

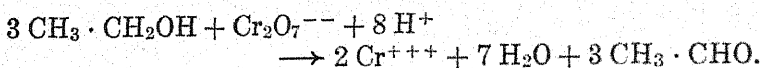


The quantity of base used in the reaction is determined by titration, and the corresponding quantity of the aldehyde is calculated on the basis of the equation.

Qualitatively formaldehyde may be detected by mixing the solution to be tested with an equal volume of milk and a few drops of ferric chloride. Concentrated sulfuric acid is then carefully introduced so as to form a layer below the mixture. A violet ring at the juncture of the two liquid layers indicates the presence of formaldehyde. A more sensitive test, rec-

ommended by Schryver, is made as follows: To 10 cc. of the solution to be analyzed add 2 cc. of 1 per cent solution of phenylhydrazine hydrochloride (freshly prepared and filtered), 1 cc. of 5 per cent solution of potassium ferricyanide, and 5 cc. of concentrated hydrochloric acid. A red color develops immediately if formaldehyde is present.

*Acetaldehyde*,  $\text{CH}_3 \cdot \text{CHO}$ , a colorless, inflammable liquid (m.p.  $-123.5^\circ$ , b.p.  $20.2^\circ$ , sp. gr. 0.781), is usually prepared by allowing a mixture of alcohol and sulfuric acid to drop into a solution of potassium dichromate:

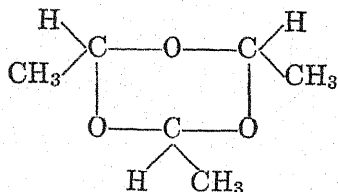


Conversion of the alcohol to acetic acid is prevented by continuous distillation, the aldehyde being removed as fast as formed. The aldehyde is miscible in all proportions with water, alcohol, and ether. On exposure to air it slowly takes up oxygen, forming acetic acid. In addition to the general methods for preparing aldehydes a few special methods for making acetaldehyde have been employed with success. The aldehyde can be made from acetylene. The reaction is carried out by passing acetylene through a suspension of a mercuric salt in dilute sulfuric acid. Ethylene, also, may be used as a source of acetaldehyde. The oxidation of ethylene gives rise to glycol,  $\text{CH}_2\text{OH}-\text{CH}_2\text{OH}$ , which loses water when warmed with zinc chloride and forms acetaldehyde. The elimination of water probably results in the transient existence of  $\text{CH}_2 : \text{CHOH}$ ; but a hydroxyl group does not, as a rule, remain attached to a doubly linked carbon atom. The hydroxyl hydrogen migrates to the adjacent carbon, leaving, in this case,  $\text{CH}_3 \cdot \text{CHO}$ .

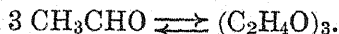
At  $400^\circ$  acetaldehyde begins to decompose into methane and carbon monoxide, and at  $600^\circ$  decomposition is rapid, carbon, hydrogen, and water vapor appearing among the products formed.

Acetaldehyde polymerizes very readily. A few drops of concentrated sulfuric acid induce a condensation that proceeds with almost explosive violence. When the action ceases, the acetaldehyde (b.p.  $20.2^\circ$ ) has been converted into a liquid of much greater density and boiling more than  $100^\circ$  higher (b.p.  $124^\circ$ , sp. gr. 0.994). The formula of the new compound, known as paracetaldehyde, is  $(\text{C}_2\text{H}_4\text{O})_3$ . It fails to exhibit the ordinary aldehyde reactions. For example, it does not reduce ammoniacal silver solution nor does it resinify with alkalis. On

this account it is assumed that the  $\text{—CHO}$  groups are involved in the union of the three molecules in such a way as to destroy the aldehyde structure. It fails, also, to react with sodium, so that there can be no hydroxyl groups present. The following constitutional formula for paracetaldehyde has been proposed :



When distilled with dilute sulfuric acid, it reverts to ordinary acetaldehyde. The change is reversible and may be represented by a balanced equation :

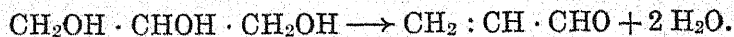


In the process of distillation the more volatile acetaldehyde escapes. The equilibrium is thereby disturbed in such a way as to promote the decomposition of the paracetaldehyde, and the entire mass gradually dissociates, yielding acetaldehyde.

Acetaldehyde yields a different polymer when cooled to a temperature below zero and treated with hydrogen chloride gas. The condensation product separates in the form of colorless needle-like crystals. On the basis of cryoscopic measurements it has been assigned the formula  $(\text{C}_2\text{H}_4\text{O})_4$ . It is called metacetaldehyde. It lacks the characteristic properties of aldehydes, sublimes at  $160^\circ$ , and at  $200^\circ$  it passes quantitatively into acetaldehyde.

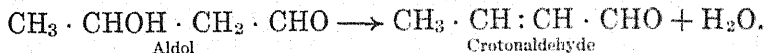
An entirely different condensation of acetaldehyde, known as the aldol condensation, has been mentioned (see page 71).

*Acrolein*, acrylic aldehyde,  $\text{CH}_2 : \text{CH} \cdot \text{CHO}$ , shares the properties of aldehydes and of unsaturated hydrocarbons. It is made by passing glycerol vapor over hot magnesium sulfate :



Acrolein is a colorless liquid (b.p.  $52^\circ$ ). It is sparingly soluble in water and it is characterized by a pungent, unpleasant odor. Acrolein combines slowly with atmospheric oxygen, forming acrylic acid,  $\text{CH}_2 : \text{CH} \cdot \text{COOH}$ .

*Crotonaldehyde*,  $\text{CH}_3 \cdot \text{CH} : \text{CH} \cdot \text{CHO}$ , a colorless liquid (b.p.  $105^\circ$ ), is made from aldol by treatment with hydrochloric acid :



Aldol may be formed and dehydrated in one operation by warming acetaldehyde with dilute hydrochloric acid. Crotonaldehyde is often made in this way.

*Acetone*,  $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_3$ , is a colorless liquid with an agreeable odor and burning taste (b.p.  $56.1^\circ$ , m.p.  $-94.3^\circ$ ). It is obtained by distilling calcium acetate, or it may be produced, along with methyl alcohol, acetic acid, and other products, by distilling wood. Glucose, a sugar obtained from starch, is another commercial source of acetone. Certain bacteria cause a fermentation of glucose that gives rise to acetone, normal butyl alcohol, and other products. A different ferment derived from yeast converts glucose into ethyl alcohol.

Acetone reacts with the Grignard reagent and with sodium bisulfite, phosphorus pentachloride, hydrocyanic acid, hydroxylamine, and phenylhydrazine as indicated under the discussion of general reactions of aldehydes and ketones. The principal uses of acetone depend upon its capacity to dissolve a great variety of organic compounds. It is employed in the manufacture of smokeless powders and in the preparation of lacquers and paint removers.

## MONOBASIC ACIDS AND THEIR DERIVATIVES

The saturated monobasic acids may be regarded as derivatives of the paraffin hydrocarbons in which one hydrogen atom has been replaced by the carboxyl group,  $\text{—COOH}$ . They correspond to the general formula  $\text{C}_n\text{H}_{2n+1}\text{COOH}$  or  $\text{RCOOH}$ .

The lower members of the series are mobile, colorless liquids, having pungent odors and a sour taste; the intermediate members are oily liquids sparingly soluble in water; and those of higher molecular weight are odorless solids insoluble in water but readily soluble in alcohol, chloroform, or ether. The lower members distill without decomposition. Those of higher molecular weight decompose before boiling. The acids of this series having odd numbers of carbon atoms are rarely found in nature; those having even numbers of carbon atoms are abundant.

The acids of lowest molecular weight have the highest densities, they are the best electrolytes, the most soluble in water, and the most volatile. These qualities are, no doubt, associated with their relatively high per cent of oxygen. As the molecular weights increase the influence of the two oxygen atoms becomes less marked, and in chemical and physical properties the acids become more like the corresponding hydrocarbons. Formic acid is by far the strongest one of the series.

The ionization of an acid in aqueous solution is represented by the equation



The dissociation constant of an acid,  $K_a$ , is defined by the equation

$$K_a = \frac{(\text{RCOO}^-)(\text{H}^+)}{(\text{RCOOH})}.$$

The terms within parentheses represent the concentrations of the ions and of the undissociated molecules, in moles per liter, when equilibrium is established. The values of  $K_a$  and of other physical constants for some of the saturated monobasic acids are given in the following table:

| ACID                        | FORMULA  | MELTING POINT | BOILING POINT | $K_a \times 10^5$ | PER CENT IONIZED IN 0.1 N SOLUTION |
|-----------------------------|--|---------------|---------------|-------------------|------------------------------------|
| Formic . . . . .            | HCOOH  | + 8.6°        | 100.7°        | 21.4              | 4.52                               |
| Acetic . . . . .            | CH <sub>3</sub> COOH                                     | 16.7°         | 118.1°        | 1.82              | 1.34                               |
| Propionic . . . . .         | CH <sub>3</sub> CH <sub>2</sub> COOH                     | - 22.0°       | 141.1°        | 1.34              | 1.13                               |
| Butyric (normal) . . . . .  | CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> COOH     | - 7.9°        | 163.5°        | 1.49              | 1.22                               |
| Butyric (iso) . . . . .     | (CH <sub>3</sub> ) <sub>2</sub> CHCOOH                   | + 79°         | 154.4°        | 1.45              | 1.20                               |
| Valeric (normal) . . . . .  | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> COOH     | - 58.5°       | 187°          | 1.45              | 1.20                               |
| Valeric (iso) . . . . .     | (CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> COOH   | - 51°         | 176.7°        | 1.70              | 1.29                               |
| Methylethylacetic . . . . . | (CH <sub>3</sub> )(C <sub>2</sub> H <sub>5</sub> )CHCOOH | - 80°         | 174°          | 1.69              | 1.29                               |
| Trimethylacetic . . . . .   | (CH <sub>3</sub> ) <sub>3</sub> CCOOH                    | + 35.5°       | 163.8°        | 0.98              | 0.99                               |
| Caproic (normal) . . . . .  | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> COOH     | - 5.2°        | 202.7°        | 1.40              | 1.18                               |

The degree of dissociation of an acid is influenced by its structure and by its mass and composition. The most important single factor is the nature of the atoms or groups attached to the  $\alpha$ -carbon atom. (The  $\alpha$ -carbon atom is the one adjacent to the carboxyl group.) The changes produced in the dissociation constant of an acid by making certain  $\alpha$  substitutions are shown in the following table:

| ACID                      | FORMULA                              | $K_a$                 |
|---------------------------|--------------------------------------|-----------------------|
| Acetic . . . . .          | CH <sub>3</sub> COOH                 | $1.82 \times 10^{-5}$ |
| Chloroacetic . . . . .    | CH <sub>2</sub> ClCOOH               | $1.55 \times 10^{-3}$ |
| Bromoacetic . . . . .     | CH <sub>2</sub> BrCOOH               | $1.38 \times 10^{-3}$ |
| Iodoacetic . . . . .      | CH <sub>2</sub> ICOOH                | $7.1 \times 10^{-4}$  |
| Dichloroacetic . . . . .  | CHCl <sub>2</sub> COOH               | $5.14 \times 10^{-2}$ |
| Trichloroacetic . . . . . | CCl <sub>3</sub> COOH                | $12.1 \times 10^{-1}$ |
| Cyanoacetic . . . . .     | CH <sub>2</sub> CNCOOH               | $3.7 \times 10^{-3}$  |
| Hydroxyacetic . . . . .   | CH <sub>2</sub> OHCOOH               | $1.52 \times 10^{-4}$ |
| Aminoacetic . . . . .     | CH <sub>2</sub> NH <sub>2</sub> COOH | $1.8 \times 10^{-10}$ |

The concentration of the hydrogen ions in an acid solution is measured by means of a hydrogen electrode or by the use of colored indicators.\* The total quantity of acid in the solution is determined by titration with a base.

1. A 0.1 N solution of acetic acid is 1.34 per cent ionized. Find the value of  $K_a$ .

$$1.34 \times 10^{-2} \times 0.1 = 1.34 \times 10^{-3} = \text{moles of } H^+ \text{ per liter.}$$

$$1.34 \times 10^{-3} = \text{moles of } CH_3COO^- \text{ per liter.}$$

$$K_a = \frac{(H^+)(CH_3COO^-)}{(CH_3COOH)} = \frac{(1.34 \times 10^{-3})^2}{0.1 - (1.34 \times 10^{-3})} = \frac{1.8 \times 10^{-6}}{(10 \times 10^{-2}) - (.134 \times 10^{-2})}$$

$$= \frac{1.8 \times 10^{-6}}{9.87 \times 10^{-2}} = \frac{18 \times 10^{-7}}{9.87 \times 10^{-2}} = 1.82 \times 10^{-5}.$$

\* W. M. Clark, The Determination of Hydrogen Ions. Williams and Wilkins Company, Baltimore.

To find the  $pH$  of such a solution we have

$$pH = \log \frac{1}{(H^+)} = \log \frac{1}{1.34 \times 10^{-3}} = -\log (1.34 \times 10^{-3}).$$

$$\log 1.34 = 0.127$$

$$\log 10^{-3} = -3.000$$

$$\log 1.34 + \log 10^{-3} = -2.873$$

$$-\log (1.34 \times 10^{-3}) = 2.873 = pH \text{ of } 0.1 \text{ } N \text{ solution of acetic acid.}$$

2. Find the per cent of formic acid which is dissociated in a 0.2  $N$  solution.

$$K_a = 2.14 \times 10^{-4}.$$

$$K_a = \frac{(H^+)(HCOO^-)}{(HCOOH)} = \frac{(H^+)^2}{(HCOOH)} = \frac{(H^+)^2}{0.2 - (H^+)*}.$$

$$\frac{(H^+)^2}{0.2 - (H^+)} = 2.14 \times 10^{-4},$$

$$(H^+)^2 = (4.28 \times 10^{-5}) - (2.14 \times 10^{-4})(H^+),$$

$$(H^+)^2 + (2.14 \times 10^{-4})(H^+) - (0.428 \times 10^{-4}) = 0,$$

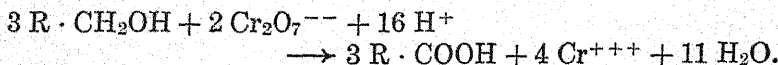
$$(H^+) = \frac{-(2.14 \times 10^{-4}) \pm \sqrt{(2.14 \times 10^{-4})^2 + (1.712 \times 10^{-4})}}{2},$$

$$(H^+) = 6.44 \times 10^{-3}.$$

$$\text{Fraction ionized} = \frac{6.44 \times 10^{-3}}{0.2} = 0.0322.$$

$$\text{Per cent ionized} = 3.22 \%.$$

**Preparation.** 1. The best general method for making the saturated monobasic acids is the oxidation of primary alcohols. Potassium dichromate and sulfuric acid are commonly employed to supply the oxygen required.



2. Unsaturated acids are converted into saturated acids by reduction. This is accomplished by means of sodium amalgam or by zinc in acid or alkaline solution or by the action of free hydrogen in the presence of a catalyst such as finely divided nickel or palladium. The reaction is of technical importance in the conversion of oleic acid into stearic acid.

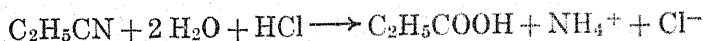
\* In weaker acids ( $K_a < 10^{-4}$ ) the value of  $(H^+)$  is so small in comparison with the total acid concentration that this term may be neglected. The calculation would be simplified by using

$$\frac{(H^+)^2}{0.2} = 2.14 \times 10^{-4},$$

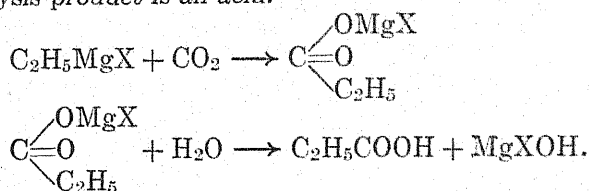
but in this case such an approximation would introduce an appreciable error (see page 142).



3. An alkyl cyanide, or nitrile, is hydrolyzed when heated with an aqueous solution of an acid as indicated by the following equation :

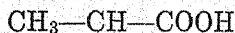


4. When carbon dioxide is passed into an ether solution of an alkyl magnesium halide (Grignard reagent), an addition product is formed which is readily hydrolyzed by cold water. The hydrolysis product is an acid.

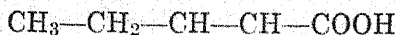


The acid is extracted with ether and obtained in the free state by evaporating the solvent.

**Nomenclature.** Special names have been given to all the common acids, and well-established names, though often meaningless, are not easily replaced by scientific nomenclature. A complete system for naming the acids is based upon the names of the paraffin hydrocarbons having the same number of carbon atoms in the longest continuous chain. The final *e* of the name of the hydrocarbon is changed to *oic*. Thus  $\text{CH}_3 \cdot \text{COOH}$  is ethanoic acid;  $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{COOH}$  is propanoic acid, etc. Positions of side chains are indicated by numerals preceding the names of the groups. The carboxyl carbon is usually numbered 1. The letters of the Greek alphabet are often used to designate a particular position in the chain. The lettering begins with the carbon atom next to the carboxyl group :



2-Methylpropanoic acid  
or  
 $\alpha$ -Methylpropanoic acid



2-Amino-3-methylpentanoic acid  
or  
 $\alpha$ -Amino- $\beta$ -methylpentanoic acid

**Acyl radicals.** The univalent residual group that would be left if the hydroxyl in the carboxyl group were eliminated from an acid is called an acyl radical. Acyl radicals do not exist in the free state, but they are present in many types of

acid derivatives. They are named from the corresponding acids by changing the final *ic* to *yl*.

| ACIDS               |                                      | ACYL RADICALS       |                                     |
|---------------------|--------------------------------------|---------------------|-------------------------------------|
| Formic . . . . .    | H · COOH                             | Formyl . . . . .    | H · CO—                             |
| Acetic . . . . .    | CH <sub>3</sub> · COOH               | Acetyl . . . . .    | CH <sub>3</sub> · CO—               |
| Propionic . . . . . | C <sub>2</sub> H <sub>5</sub> · COOH | Propionyl . . . . . | C <sub>2</sub> H <sub>5</sub> · CO— |

### ACIDS OF LOW MOLECULAR WEIGHT

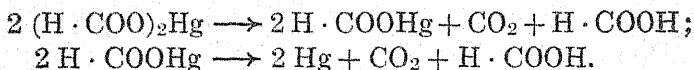
*Formic acid*, H · COOH, differs from all other members of the series in being easily oxidized. This is due to the fact that it is

an aldehyde as well as an acid,  $\text{H}-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$ . It is decomposed

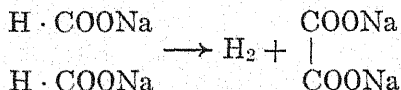
by concentrated sulfuric acid, slowly when cold but with rapid effervescence at high temperatures, the products being carbon monoxide and water. Many of the salts of formic acid are decomposed by heat. Mercury and silver formates when warmed yield the free metals, carbon dioxide and formic acid, half of the acid being liberated and half oxidized. With silver formate the reaction is



With mercuric formate the change takes place in two stages, mercurous formate being first produced; and from that salt free mercury is liberated on further heating:



When heated to 400°, sodium formate yields hydrogen and sodium oxalate:



Formic acid is a colorless liquid with an irritating odor. It produces a burning sensation when in contact with the skin, and unless promptly removed it forms blisters. It forms a constant boiling mixture with water (77.5 per cent acid, b.p. 107.1°) and therefore cannot be freed from water by distillation alone. It occurs in the body fluids of ants and bees.

Anhydrous formic acid melts at  $8.4^{\circ}$ , boils at  $100.7^{\circ}$ , and has a density of  $1.220\frac{20}{4}$ . The salts of formic acid (*formates*) are soluble in water; the silver, copper, and lead salts, however, are only sparingly soluble.

When heated alone, to a temperature of  $160^{\circ}$ , or higher, formic acid decomposes into carbon dioxide and hydrogen:



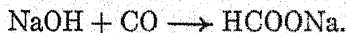
This reaction is catalyzed by finely divided platinum, rhodium, or palladium. With either of these catalysts the decomposition of formic acid occurs, at a measurable rate, at room temperatures.

In the presence of a dehydrating agent, such as concentrated sulfuric acid, the decomposition of formic acid results in the formation of carbon monoxide and water:



**Preparation.** Formic acid may be prepared in several ways. The following methods are commonly used:

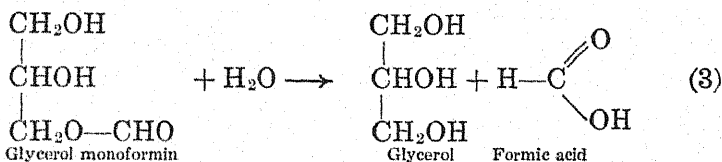
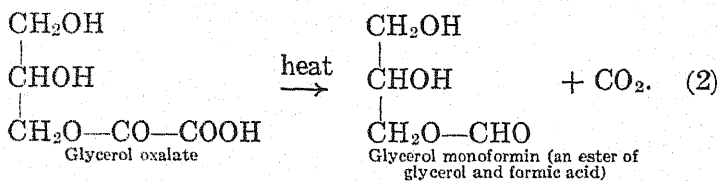
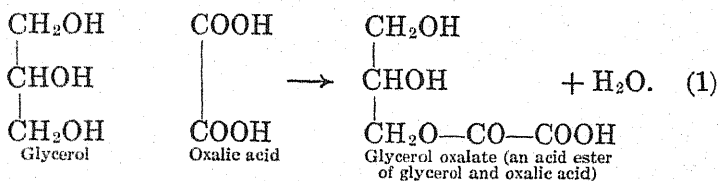
1. At temperatures between  $150^{\circ}$  and  $225^{\circ}$ , and under pressures of from six to ten atmospheres, sodium hydroxide absorbs carbon monoxide, forming sodium formate:



Free formic acid is obtained from the sodium salt by mixing the salt with sodium hydrogen sulfate and heating the dry mixture.

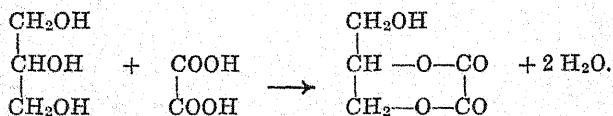
2. Formic acid may be prepared by heating a mixture of hydrated oxalic acid and glycerol. When heated alone, oxalic acid is decomposed, with the formation of water, carbon dioxide, and carbon monoxide. If, however, a glycerine solution of hydrated oxalic acid,  $\text{C}_2\text{H}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ , is heated to  $120^{\circ}$ , the principal products formed are formic acid and carbon dioxide. Under these conditions an *acid ester* of oxalic acid is formed as an intermediate product. The ester decomposes at about  $100^{\circ}$ , yielding carbon dioxide and an ester of formic acid known as glycerol monoformin. The latter is readily hydrolyzed to formic

acid and glycerol. The main reactions are indicated by the following equations:

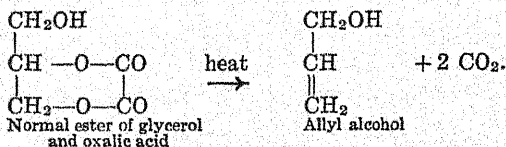


Reaction (3) is induced by the water derived from the hydrated crystals of oxalic acid and the water released in reaction (1).

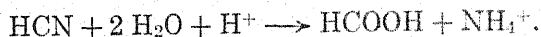
When *anhydrous* oxalic acid is heated with glycerol to a temperature of 200° or higher, allyl alcohol is formed. Under these conditions the normal glycerol ester of oxalic acid is the intermediate product.



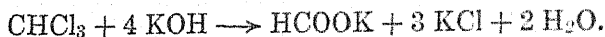
This ester is decomposed by heat with the production of carbon dioxide and allyl alcohol:



3. Formic acid is produced in the hydrolysis of hydrocyanic acid:



4. Chloroform is decomposed by hot caustic alkali, yielding a formate:



*Acetic acid*,  $\text{CH}_3\text{COOH}$ , as formed in the fermentation of fruit juice, was known to the alchemists of the sixteenth century. It was isolated from other fermentation products by Stahl (1720), and was first synthesized by Berzelius in 1814.

The anhydrous acid melts at  $16.67^\circ$  and boils at  $118^\circ$  under 760 mm. pressure. Below  $16^\circ \text{C}$ . the crystalline solid has the appearance of ice, and the pure acid is commonly called glacial acetic acid. A rise of temperature and contraction in volume occur when water is added to acetic acid, the maximum temperature effect, highest density, and maximum viscosity being produced when the solution contains equimolal quantities of the acid and water. This indicates the formation of a hydrate,  $\text{CH}_3\text{COOH} \cdot \text{H}_2\text{O}$ .

Pure acetic acid and a 43 per cent solution in water have the same density. The changes in density with dilution are indicated in the following table:

| CONCENTRATION  | SPECIFIC GRAVITY |
|----------------|------------------|
| 100% . . . . . | 1.055            |
| 90% . . . . .  | 1.071            |
| 80% . . . . .  | 1.075            |
| 70% . . . . .  | 1.073            |
| 60% . . . . .  | 1.069            |
| 50% . . . . .  | 1.062            |
| 43% . . . . .  | 1.055            |
| 40% . . . . .  | 1.052            |
| 30% . . . . .  | 1.041            |
| 20% . . . . .  | 1.028            |
| 10% . . . . .  | 1.014            |
| 0% . . . . .   | 1.000            |

Owing to the high molecular freezing-point constant for acetic acid\* and the low molecular weight of water, a very small quantity of water causes a considerable change in the freezing point of the acid. A freezing-point determination, therefore,

\*  $K = 3860$  (see page 464).

constitutes a satisfactory method for estimating the concentration of an acetic acid solution. The effect of dilution on the freezing point is indicated in the following table:

| CONCENTRATION   | FREEZING POINT |
|-----------------|----------------|
| 100% . . . . .  | 16.67°         |
| 99% . . . . .   | 14.80°         |
| 98% . . . . .   | 13.25°         |
| 96.2% . . . . . | 10.50°         |
| 92.6% . . . . . | 6.25°          |
| 89.2% . . . . . | 2.7°           |
| 87.0% . . . . . | -0.2°          |
| 75.4% . . . . . | -12.8°         |
| 70% . . . . .   | -18.1°         |
| 60% . . . . .   | -26.6°         |
| 47% . . . . .   | -19.3°         |
| 10% . . . . .   | -3.4°          |

Acetic acid and many of its salts and esters are of great technical importance. Cellulose acetate is used in one process of making artificial silk, in the manufacture of photographic films, and in the preparation of safety glass. Windshields and windows for automobiles are made by pressing a thin sheet of cellulose acetate between two sheets of ordinary glass. Basic lead acetate is used in the manufacture of paints (white lead). Paris green, which is used as an insecticide, is a mixture of copper acetate and copper arsenite,  $\text{Cu}(\text{C}_2\text{H}_3\text{O}_2)_2$  and  $\text{Cu}(\text{AsO}_3)_2$ . Acetates of chromium, iron, and aluminum are used as mordants in dyeing cotton. Acetic acid is used also in the synthesis of some artificial flavors and perfumes and in the manufacture of paper.

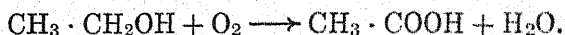
The acid is stable toward oxidizing and reducing agents, and on that account it is frequently used as a solvent for compounds that are to be oxidized by dichromate or permanganate ions. Glacial acetic acid is hygroscopic. It dissolves in water with an evolution of heat and contraction in volume, the density of the solution gradually increasing until a solution containing 78 per cent of acid is produced. Beyond that point the density decreases as indicated in the table on page 88.

Acetic acid is an excellent solvent for many organic compounds. It dissolves readily in the common organic solvents, and in most solvents it exists in the form of double molecules.

This state of aggregation is detected by molecular-weight determinations and is known as association. Even in the vapor phase, at temperatures below 150°, there is considerable association.

Several methods have been developed for manufacturing acetic acid. It is used in large quantities not only as a laboratory reagent but as the principal acid component of vinegar. The most important commercial methods of preparation are the oxidation of ethyl alcohol and the distillation of wood.

**Oxidation of alcohol.** Large wooden tanks are filled with beechwood shavings inoculated with mother of vinegar (*Mycoderma aceti*). Dilute alcohol (6 to 10 per cent) is allowed to percolate through the shavings against a countercurrent of air. The alcohol is distributed in thin layers over the shavings, exposing large surfaces to the air. The shavings also preserve a porous structure in the tanks, allowing free passages for air, and they constitute a suitable home for the growth and propagation of the oxidizing bacteria. The reaction is a simple oxidation:



The mixture of alcohol and acetic acid drawn from the bottom of one tank is transferred to the top of a similar tank, and so on until the conversion is nearly complete. The product obtained by this process is approximately a 6 per cent solution of acetic acid in water. Glacial acetic acid is made by neutralizing the dilute acid with lime and evaporating the water. The salt, calcium acetate, is then treated with an equivalent quantity of sulfuric acid. The acetic acid liberated in this way is distilled from the mixture.

**Distillation of wood.** Wood is distilled from large iron retorts, the temperature being gradually raised to 450° or 500°. Between 160° and 300° a liquid distillate, pyroligneous acid, is produced. It consists chiefly of water, acetic acid, methyl alcohol, and acetone. After the addition of lime the volatile liquids are distilled off, leaving a solid residue of calcium acetate. An equivalent quantity of sulfuric acid is then added, and the more volatile acetic acid is removed by distillation. To remove the small amount of water contained in the distillate the liquid is cooled until glacial acetic acid crystallizes. The crystalline mass is then removed from the mother liquor and allowed to melt at the temperature of the room.

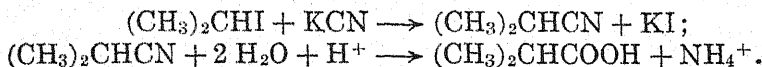


Butyric acids. According to the structure theory two acids corresponding to the formula  $C_3H_7COOH$  should exist, and two are known.

Normal butyric acid,  $CH_3-CH_2-CH_2-COOH$  (b.p.  $162.5^\circ$ ), occurs as an ester in butter and in the free state in rancid butter, in Limburger cheese, and in some secretions of the body, especially in perspiration. It is soluble in water, but separates as an oil when the aqueous solution is saturated with calcium chloride. All soluble members of this series, except formic acid and acetic acid, may be salted out of solution.

Isobutyric acid,  $\begin{matrix} CH_3 \\ CH_3 \end{matrix} \rangle CH-COOH$  (b.p.  $154^\circ$ ), is found both

free and combined in many plants but never in very large quantities. It is prepared by hydrolyzing isopropyl cyanide. Isopropyl iodide is the most convenient laboratory source of the cyanide:



The calcium salt of isobutyric acid is more soluble in hot than in cold water. Normal calcium butyrate is more soluble in cold than in hot water.

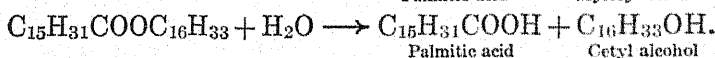
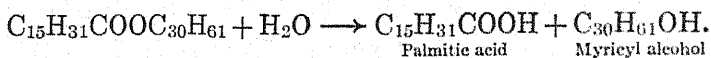
### HIGHER ACIDS

Palmitic acid,  $C_{15}H_{31}COOH$ , and stearic acid,  $C_{17}H_{35}COOH$ , occur together as glycerol esters in the natural fats. They are liberated from the glycerol by boiling the fat with an acid. Their salts are formed when the fat is saponified by boiling with alkalis. These acids are white solids, amorphous and waxlike, as ordinarily prepared, but easily crystallized from alcohol or other organic solvents.

When obtained by hydrolysis of fats, they are mixed with oleic acid — an unsaturated compound belonging to a different series. The liquid, oleic acid, is pressed out of the mixture. Stearic and palmitic acids may be separated by adding magnesium acetate to an alcoholic solution of the mixture. Magnesium stearate precipitates, and from the salt the free acid may be obtained by boiling it with hydrochloric acid. The free stearic acid solidifies when cold and floats on the surface of the water.

Oleic acid may be separated from stearic and palmitic acids by forming the lead salts and extracting the mixed salts with ether. Lead oleate is soluble in ether. The free acid is obtained from the salt by treatment with sulfuric acid.

*Palmitic acid*, *n*-hexadecylic acid (m.p. 62°), is usually obtained from olive oil, which is composed, almost exclusively, of the glycerol esters of palmitic and oleic acids. Myricyl palmitate,  $C_{15}H_{31}COOC_{30}H_{61}$ , the principal component of beeswax, is another source of this acid. Spermaceti, a white waxy substance found in the head of the sperm whale, is composed chiefly of cetyl palmitate,  $C_{15}H_{31}COOC_{16}H_{33}$ . Myricyl and cetyl palmitates belong to the class of compounds known as esters. They are hydrolyzed by boiling with an acid, forming the free palmitic acid together with myricyl and cetyl alcohols respectively:

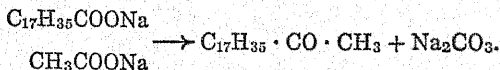


Palmitic acid has been synthesized by oxidizing cetyl alcohol.

*Stearic acid*, *n*-octodecylic acid, melts at 69°. As ordinarily prepared, it is a colorless, soft, amorphous substance. It is not difficult to obtain it in crystalline form by slowly cooling a hot saturated alcoholic solution of the acid.

Stearic acid is a normal, or straight-chain, compound.

Dry distillation of a mixture of salts of stearic and acetic acids results in the formation of margarylmethyl ketone:



On oxidation the ketone yields acetic acid,  $CH_3COOH$ , and margoric acid,  $C_{16}H_{33}COOH$ . This proves that the margaryl radical,  $C_{17}H_{35}$ , has the structure  $C_{16}H_{33}-CH_2-$ . From salts of margoric and acetic acids palmitylmethyl ketone,  $C_{16}H_{33} \cdot CO \cdot CH_3$ , has been made. When oxidized this ketone yields acetic acid and palmitic acid,  $C_{15}H_{31}COOH$ , showing that the structure of the palmityl radical is  $C_{15}H_{31}-CH_2-$ . This process has been continued step by step from stearic acid back to capric acid,  $C_9H_{19}COOH$ , and the latter has been synthesized from lower members of the acetic acid series. It is known to have a straight chain of carbon atoms, its formula being

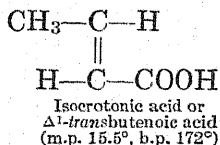
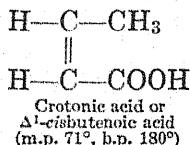


Hence we know that stearic acid is a straight-chain compound having the formula  $CH_3 \cdot (CH_2)_{16} \cdot COOH$ .

## UNSATURATED ACIDS

*Acrylic acid.* The simplest of the unsaturated monobasic acids, acrylic or propenoic acid, has the formula  $\text{CH}_2=\text{CH}-\text{COOH}$ . It melts at  $8^\circ$ , boils at  $140^\circ$ , and dissolves in water in all proportions. It is a stronger acid than the corresponding saturated compound (acrylic acid,  $K_a = 5.76 \times 10^{-5}$ ; propionic acid,  $K_a = 1.34 \times 10^{-5}$ ). Acrylic acid is made from  $\beta$ -bromopropionic acid by treatment with a hot alcoholic solution of potassium hydroxide or from  $\beta$ -hydroxypropionic acid through the action of a dehydrating agent.

*Crotonic acids.* There are four acids corresponding to the formula  $\text{C}_3\text{H}_5\text{COOH}$ . One of them is  $\alpha$ -methylacrylic acid with the structure  $\text{CH}_2=\text{C}(\text{CH}_3)-\text{COOH}$ . Another, called vinylacetic acid, has the formula  $\text{CH}_2=\text{CH}-\text{CH}_2-\text{COOH}$ . The other two acids of this group are geometrical isomers of the type described on page 25. They correspond to the following structural formulas:

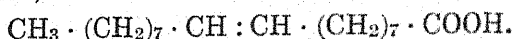


The symbol  $\Delta^1$  indicates that the double bond is between the first and the second carbon atom beyond the carboxyl group. Vinylacetic acid is  $\Delta^2$ -butenoic acid. The name of the acid having the structure  $\begin{array}{c} \text{CH}_3 \\ \searrow \\ \text{C}=\text{CH}-\text{COOH} \\ \nearrow \\ \text{CH}_3 \end{array}$  is 3-methyl- $\Delta^1$ -butenoic acid or  $\beta$ ,  $\beta$ -dimethylacrylic acid.

The inconsistency in the first name is due to the unfortunate practice of beginning with the carbon atom next to the carboxyl group in numbering the atoms for the purpose of defining the position of a double or triple bond. For other purposes the numbering begins with the carboxyl carbon.

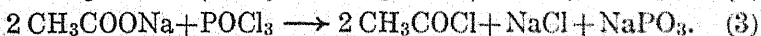
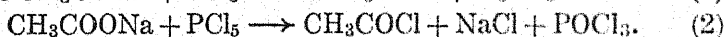
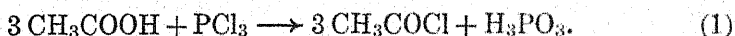
*Oleic acid.* Oleic acid,  $\text{C}_{17}\text{H}_{33}\text{COOH}$ , is obtained by hydrolyzing olive oil and other vegetable oils. It is a colorless and odorless oily liquid. It melts at  $14^\circ$  and decomposes if distilled under atmospheric pressure. Oleic acid can be reduced to stearic acid by hydrogen in contact with finely divided nickel or oxidized to dihydroxystearic acid by permanganate ion. A trace of nitrous acid converts oleic acid into elaidic acid. Oleic and

elaïdic acids are stereoisomers corresponding to crotonic and isocrotonic acids. When oxidized by dichromate ion, oleic acid yields pelargonic acid,  $C_8H_{17}COOH$ , and azelaic acid,  $COOH \cdot (CH_2)_7 \cdot COOH$ . Since unsaturated compounds usually break at the position of the double bond, we infer, from this reaction, that the formula of oleic acid is

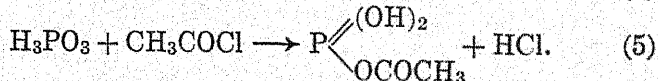
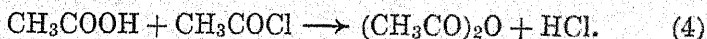


### ACID CHLORIDES

Chlorine is substituted for the hydroxyl in the carboxyl group when an acid is treated with phosphorus trichloride or phosphorus pentachloride or when the salt of an acid is treated with phosphorus pentachloride or phosphorus oxychloride. The substitution product,  $R \cdot CO \cdot Cl$ , is known as an acid chloride. The corresponding bromides may be formed in the same way by using the phosphorus compounds of bromine. Typical reactions are indicated by the following equations:



These equations do not represent quantitative reactions. It is obvious that part of the acid chloride will be formed according to equation (3) when  $PCl_5$  acts on a salt, for  $POCl_3$ , one of the reaction products in (2), can also act upon the salt. Equation (1) fails to account for the hydrogen chloride which is formed in abundance when phosphorus trichloride acts upon acetic acid. Brooks\* has proved that the hydrogen chloride is formed in secondary reactions between the acid chloride and acetic acid and between the acid chloride and phosphorous acid:

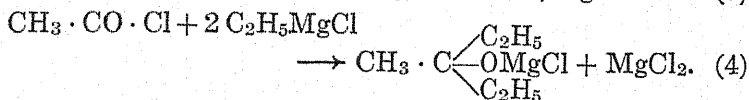
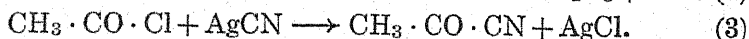
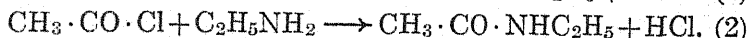
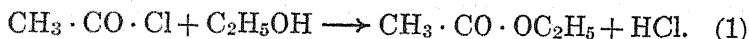


The acid chlorides having fewer than sixteen carbon atoms are liquids. The lower members fume in moist air and boil at low temperatures. They all react with water, forming the corresponding organic acid and hydrochloric acid. They react readily with alcohols, amines, alkyl magnesium halides, am-

\* Benjamin T. Brooks, *J. Am. Chem. Soc.*, 34, 492 (1912).

monia, salts of organic acids, and other reagents. They are useful, therefore, as sources of esters, amides, ketones, and acid anhydrides.

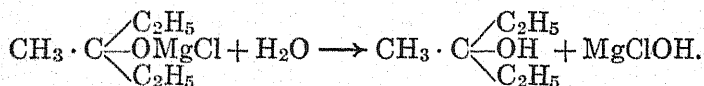
Typical reactions of the acid chlorides are represented by the following equations:



On hydrolysis, the product formed in equation (3) yields a salt of an  $\alpha$ -ketonic acid,

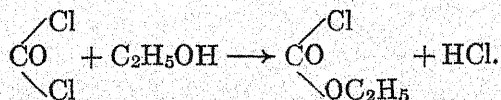


and the compound formed in the reaction represented by equation (4) yields a tertiary alcohol,

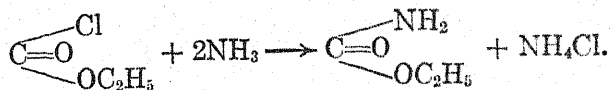


*Formyl chloride*,  $\text{H} \cdot \text{COCl}$ , has not been isolated in a pure state, for it decomposes into hydrogen chloride and carbon monoxide. In many cases, however, a mixture of  $\text{HCl}$  and  $\text{CO}$  responds to the tests one would expect to obtain with the chloride of formic acid, and this mixture is often called formyl chloride.

*Phosgene*, or carbonyl chloride,  $\text{COCl}_2$  (a derivative of carbonic acid), is made by the direct addition of chlorine to carbon monoxide under the catalytic influence of light or charcoal. The liquid boils at  $8^\circ$ . It is extremely poisonous and has been used extensively in gas warfare. It is very soluble in benzene and in toluene. It fumes in moist air, forming carbon dioxide and hydrogen chloride, and is decomposed by alcohol, with the formation of hydrogen chloride and chloroformic ester:

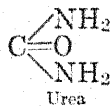
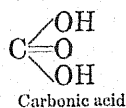


Urethane, a valuable hypnotic, is prepared from chloroformic ester by treatment with ammonia:



Urethane is a colorless crystalline body (m.p.  $50^\circ$ , b.p.  $180^\circ$ ) having a faint odor. It is an ester of carbamic acid.

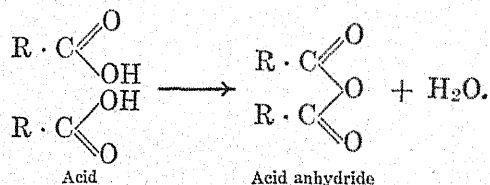
Carbamic acid has the formula  $\begin{array}{c} \text{NH}_2 \\ \diagup \\ \text{C}=\text{O} \\ \diagdown \\ \text{OH} \end{array}$ . Notice its relationship to carbonic acid and to urea:



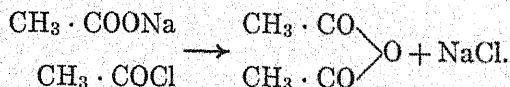
Carbamic acid has not been obtained in the free state. Many of its salts and esters are known.

### ACID ANHYDRIDES

The removal of one molecule of water from two molecules of a monobasic acid results in the formation of an acid anhydride:

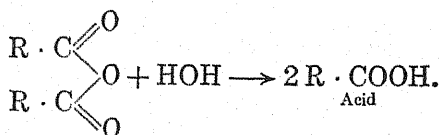
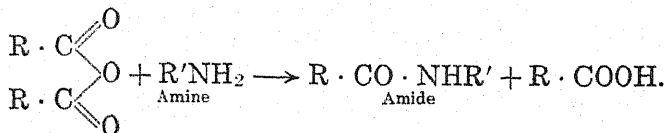
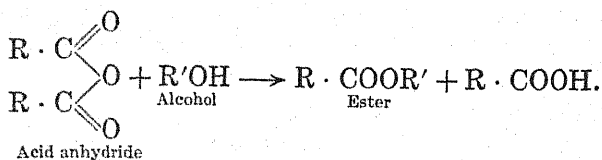


In some cases the dehydration may be accomplished by warming the acid with phosphorus pentoxide; but the result is usually achieved by other means. An acid anhydride may be made by distilling a mixture of an acid chloride and a salt of the acid. Acetic anhydride is easily prepared by this method:



**Properties.** The anhydrides of low molecular weight are colorless liquids; the higher members are solids. Although they

are less reactive than the acid chlorides, they combine with alcohols, amines, and water, as do the acid chlorides, yielding esters, amides, and acids respectively:



With metallic oxides and hydroxides the anhydrides act like the free acids in forming salts. The lower members are more reactive than those of high molecular weight. A few of the solid anhydrides may be crystallized from water without reverting to the hydrated form.

The anhydride of formic acid has never been prepared. When treated with a dehydrating agent, a molecule of water is eliminated from one molecule of formic acid, and carbon monoxide is formed. Carbon monoxide can hardly be regarded as a true anhydride of the acid, for it does not dissolve in water with the regeneration of the acid. The gas does dissolve, however, in molten metallic hydroxides, forming salts of formic acid.

### ESTERS

Alcohols and acids combine, with the elimination of water and the formation of compounds known as esters. The reaction between acetic acid and ethyl alcohol is typical:

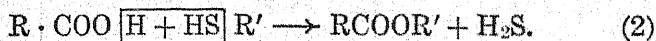
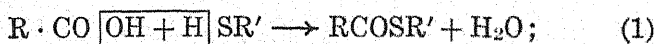


The equation reminds one of the neutralization of an acid by a base. The resemblance, however, is only formal. Alcohol is



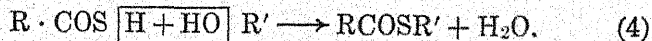
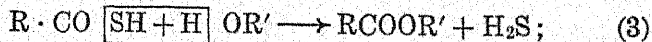
not a base, and the reaction indicated above is not ionic. Ionization is favored by the presence of water, but this reaction goes best under anhydrous conditions. It can be stopped by the addition of water to the mixture. There is other evidence that in the formation of water between the two reagents the hydroxyl comes from the acid and the hydrogen from the alcohol. A mixture of hydrochloric and acetic acids, for example, acts upon alcohol to form ethyl acetate and practically no ethyl chloride. If ethyl chloride were formed the hydrogen would necessarily come from the hydrochloric acid and the hydroxyl from the alcohol, but in forming ethyl acetate the hydrogen may be furnished by the alcohol and the hydroxyl group by the acid or vice versa. The experimental fact is that when hydrochloric acid and acetic acid are mixed and allowed to compete for alcohol molecules the acetic acid — the only one of the acids that can yield a hydroxyl group — is the one that is esterified.

An analogous reaction with mercaptans throws some light on the question. Two possible courses for the action of acids and mercaptans are represented in the equations



If the acid yields the hydroxyl group, as indicated by the first equation, water would be eliminated. If the acid supplies the hydrogen atom, as shown in the second equation, hydrogen sulfide would be liberated. The reaction ordinarily proceeds according to the first equation, splitting off water rather than hydrogen sulfide, indicating that in the formation of thioesters the hydroxyl group is removed from the acid. However, there are exceptions to this rule.

Similarly the thiol acids,  $RCOSH$ , may react with alcohols in either of two ways:



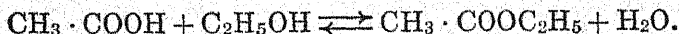
All of the possibilities represented by the four equations shown above have been realized. Some acids and alcohols react mainly in one way and other mixtures react in the opposite way. Thiolacetic acid,  $CH_3COSH$ , reacts with ethyl alcohol, yielding

both hydrogen sulfide and water. In this reaction 78 per cent of the molecules follow the course indicated in equation (3) and 22 per cent react as indicated in equation (4). When thiolacetic acid is mixed with isopropyl alcohol the products formed are  $\text{CH}_3\text{COOC}_3\text{H}_7$  and  $\text{H}_2\text{S}$  exclusively, but the same acid reacts with triphenyl carbinol,  $(\text{C}_6\text{H}_5)_3\text{COH}$ , forming  $\text{CH}_3\text{COSC}(\text{C}_6\text{H}_5)_3$  and  $\text{H}_2\text{O}$  only. For the details of experiments in this field consult the papers listed below.\*

Esters occur in great abundance in nature. All vegetable and animal fats and oils belong to this class of compounds, and many of the flavors and perfumes of fruits and flowers are due to esters. Artificial perfumes and synthetic flavors are prepared in commercial laboratories from the lower acids and alcohols; thus, methyl alcohol and butyric acid yield an ester, methyl butyrate,  $\text{C}_3\text{H}_7\text{COOCH}_3$ , which is on the market as a substitute for the flavor of pineapple. Isoamyl acetate,  $\text{CH}_3\text{COOC}_5\text{H}_{11}$ , is known as pear oil, and octyl acetate,  $\text{CH}_3\text{COOC}_8\text{H}_{17}$ , has the odor and flavor of oranges.

Esters may be hydrolyzed by boiling them with dilute acids or alkalies, or by prolonged heating with steam, the original acid and alcohol being regenerated. Isomeric esters are easily distinguished from each other by identifying their hydrolysis products. Thus, ethyl acetate,  $\text{CH}_3\text{COOC}_2\text{H}_5$ , takes up one molecule of water and forms acetic acid,  $\text{CH}_3\text{COOH}$ , and ethyl alcohol,  $\text{C}_2\text{H}_5\text{OH}$ ; whereas the isomeric ester, methyl propionate,  $\text{C}_2\text{H}_5\text{COOCH}_3$ , when hydrolyzed, yields propionic acid and methyl alcohol.

*Ethyl acetate.* Ethyl acetate,  $\text{CH}_3 \cdot \text{COOC}_2\text{H}_5$  (b.p.  $77^\circ$ , sp. gr. 0.9028), is formed by the action of ethyl alcohol on acetic acid. It is a clear, colorless liquid with a pleasant, fruity odor. It is slightly soluble in water (8.6 parts per 100) and miscible in all proportions with alcohol or ether. Since the reaction is reversible, it is not possible to convert the acid and alcohol quantitatively into the ester. Equilibrium is established when the rate of hydrolysis is equal to the rate of ester formation:



If equimolal quantities of the acid and alcohol are used, equilibrium is reached when two thirds of the acid has been

\* Pratt and Reid, *J. Am. Chem. Soc.*, 37, 1934 (1915). Reid, *J. Am. Chem. Soc.*, 39, 1930 (1917). Stewart and McKinney, *J. Am. Chem. Soc.*, 53, 1482 (1931).

changed. The condition of equilibrium is almost independent of the temperature (65.2 per cent at  $10^\circ$ , 66.5 per cent at  $220^\circ$ ), but the rate of approach to equilibrium is greatly increased by raising the temperature.

If at the beginning of the reaction we have  $a$  moles of acid and  $b$  moles of alcohol, and if when equilibrium is established  $x$  moles of acid and of alcohol have been used in forming  $x$  moles of ester and of water, then

$$\frac{x^2}{(a-x)(b-x)} = k.$$

The numerical value of the equilibrium constant,  $k$ , may be calculated by substituting in this equation the values indicated in the last paragraph:

$$\frac{(\frac{2}{3})(\frac{2}{3})}{(\frac{1}{3})(\frac{1}{3})} = k, \text{ or } k = 4.$$

With  $k$  known, the quantity of ester that will be formed in any mixture of pure alcohol and acid may be calculated. Thus, if we begin with 1 mole of acetic acid and 2.9 moles of alcohol, equilibrium will be reached when

$$\frac{x^2}{(1-x)(2.9-x)} = 4. \text{ The conversion of acid to ester in this case amounts}$$

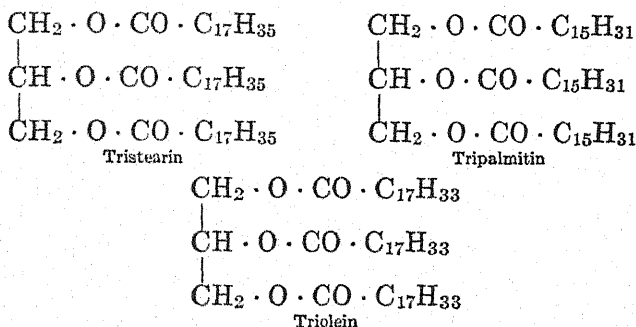
to nine tenths of the theoretical value. In actual practice the relative costs of materials determine the excess of the cheapest reagent that can be employed economically to increase the percentage yield on the basis of the more expensive reagent. Another practical means of favoring the reaction in either direction is that of withdrawing one of the products from the field of action. The activity of the water formed in esterification is reduced by the presence of sulfuric acid. If sulfuric acid is added, the active mass of water formed is kept very low, the value given for  $k$  can hardly be attained, and the reaction goes almost to completion. The equation given above cannot be applied when a dehydrating agent is present, unless the effect of such an agent in reducing the activity of the water is known.

The usual laboratory procedure for the preparation of ethyl acetate consists of mixing equal quantities of alcohol and concentrated sulfuric acid, heating to  $140^\circ$ , then adding a mixture of equal quantities of alcohol and glacial acetic acid. The alcohol and acid mixture is introduced by means of a dropping funnel at about the same rate that the ester distills over.

The mechanism of the reaction in the presence of sulfuric acid probably involves the formation of ethyl sulfuric acid,  $\text{C}_2\text{H}_5\text{HSO}_4$ , and a subsequent reaction between this compound

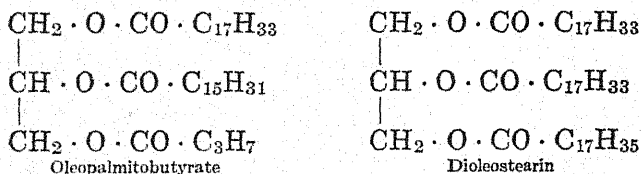
and acetic acid in which the sulfuric acid is regenerated and ethyl acetate is formed.\*

**Fats.** The fats and oils, so widely distributed in animal and vegetable tissues, are esters of the trihydric alcohol, glycerol. The principal acids combined with glycerol in the natural fats are stearic,  $C_{17}H_{35}COOH$ , palmitic,  $C_{15}H_{31}COOH$ , oleic,  $C_{17}H_{33}COOH$ , and butyric,  $C_3H_7COOH$ . One molecule of glycerol combines with three molecules of acid to form a fat. The three acid molecules may be alike or different. Stearin, palmitin, and olein are represented by the following structures:

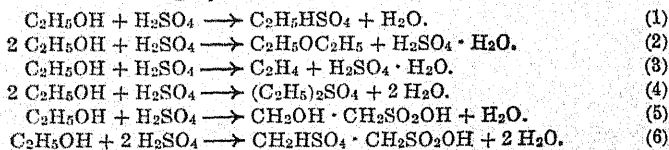


The natural fats are mixtures of these esters with smaller quantities of glycerol esters of other acids and with mixed esters, that is, esters in which two or three different acids are in combination with the same glycerol residue.

Oleopalmitobutyrate occurs in butter fat. Human fat consists, primarily, of a mixture of tripalmitin and dioleostearin.



\* Sulfuric acid acts upon alcohol in a variety of ways. The reaction products and the conditions under which they are formed have been investigated by Evans and Albertson. The following equations represent the principal reactions:



(Evans and Albertson, *J. Am. Chem. Soc.*, 39, 456 (1917).)

Butter contains glycerol esters of stearic, palmitic, oleic, myristic, capric, caprylic, caproic, and butyric acids. About 90 per cent of butter fat consists of esters of the first three acids in the list. Tristearin is the chief component of beef tallow, and triolein predominates in cottonseed oil.

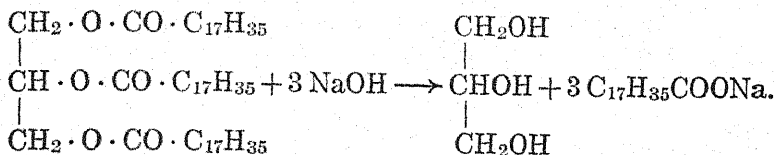
Olive oil contains from 25 per cent to 30 per cent of tripalmitin and about 65 per cent of triolein. Linseed oil contains many unsaturated fats, including esters of linoleic, linolenic, and isolinolenic acids. The last two acids are highly unsaturated. They have the formula  $C_{17}H_{29}COOH$ . The structures are unknown. Linoleic acid contains two double bonds and has the formula  $C_{17}H_{31}COOH$ . These unsaturated acids and the esters derived from them absorb oxygen from the air, forming saturated compounds. On account of this property linseed oil is a valuable component of varnishes and paints. It is called a drying oil. The oxidation product is a firm, smooth, solid substance. Linseed oil dries faster if it has been boiled with lead acetate or with litharge. These substances are practically insoluble in the oil, but enough is held in solution to catalyze the union of the oil with oxygen of the air. Linoleum is made from boiled linseed oil and ground cork.

**The iodine value.** Fats may often be identified or distinguished from each other by estimating the quantity of the unsaturated esters present. This is accomplished by measuring the iodine absorbed. Two atoms of iodine will be taken up at each double bond. A weighed quantity of fat is dissolved in chloroform and titrated with an alcoholic solution of iodine and mercuric chloride. The iodine number is the per cent of iodine absorbed, calculated on the basis of the weight of oil used, that is,  $\frac{\text{weight of iodine}}{\text{weight of fat}} \times 100$ . The iodine value of cottonseed oil is 111 to 116, and of coconut oil, 8.5 to 9.0.

**The Reichert-Meissel number.** Fatty acids of low molecular weight are soluble in water and volatile with steam. Higher members either do not distill with steam or fail to dissolve in the distillate. The quantity of ester of low molecular weight may be estimated by saponifying the fat, acidifying with sulfuric acid, distilling with steam, and titrating the cold filtered distillate with an alkali. The Reichert-Meissel number is the number of cubic centimeters of tenth normal base required to neutralize the water-soluble volatile acid found in 5 g. of fat. The Reichert-Meissel number of butter is 22 to 30; of oleomargarine, 0.5 to 1.5; and of lard, 0.3 to 0.6.

Fats may be hydrolyzed by boiling with dilute acids or alkalies or by heating with steam. The products formed are glycerol and the free fatty acids or, if boiled with alkalies,

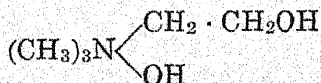
glycerol and the salts of fatty acids (soaps). Hydrolysis by an alkali is referred to as saponification.



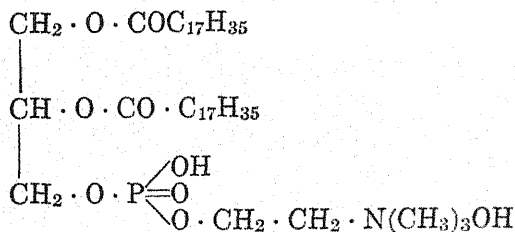
Since all natural sources of fats yield mixed esters, the soaps ordinarily manufactured are not pure salts. They are mixtures of the salts of several acids — chiefly stearic, palmitic, and oleic — in which more or less water, glycerol, and alkali are incorporated. Different soaps are made by varying the relative proportions of different fats, by using different bases, by incorporating different amounts of glycerol, and so on. Hard soaps and soap powders are made by saponifying solid fats with sodium hydroxide. Potassium salts are softer than the corresponding sodium derivatives, and soaps derived from oils are softer than those obtained from solid fats. Calcium, magnesium, and barium salts of the fatty acids are not soluble in water. When a soluble soap is added to "hard" water, a flocculent precipitate of the calcium or magnesium soap separates, and the water is "softened" as effectively as if accomplished by precipitating these metals as hydroxides by the addition of sodium hydroxide or ammonia. The use of soap for softening water is not an economical practice.

The free fatty acids are prepared in large quantities by hydrolyzing the fats with superheated steam. Stearic acid freed by pressure from the softer acids is mixed with a little paraffin to render it less brittle and is used in the manufacture of candles.

**Lecithins.** Lecithins, though less abundant than fats, occur in almost every cell of the animal organism. They are like the fats in many respects. When boiled with dilute acids, lecithins take up water, forming free fatty acids, choline, and glycerophosphoric acid. The latter is also partly hydrolyzed to phosphoric acid and glycerine, so that the ultimate hydrolysis products are the same as for the fats plus phosphoric acid and choline. Choline,



is found in combination with complex acids in the bile. The name *choline* is derived from the Greek word meaning bile. In lecithins choline is combined with phosphoric acid, forming a group which takes the place of one acid radical in the fats. The formula of distearyl lecithin is

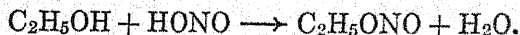


Lecithins and other lipoids (fatlike bodies) are especially abundant in nervous tissue, but they are not confined to any particular kind of tissue nor to the animal organism. They are present in small quantities in plants.

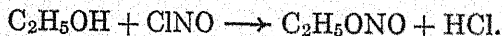
Lecithins dissolve in alcohol, chloroform, ether, benzene, and carbon disulfide. They are insoluble in water and only slightly soluble in acetone. Most of them crystallize from alcohol in thin, transparent plates, colorless or slightly yellow. A preparation of a lecithin can be made by grinding the brain of an animal with a little sand and allowing it to stand under cold ether two or three days. Acetone is then added to the clear ether extract, and lecithin is precipitated.

### ESTERS OF INORGANIC ACIDS

**Nitrous esters.** Sodium nitrite acts upon a mixture of alcohol and sulfuric acid to form the nitrous acid ester of the alcohol:



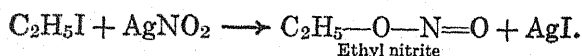
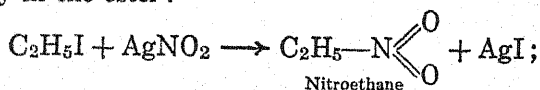
The same product may be formed from alcohol and nitrosyl chloride:



Silver nitrite acts upon many alkyl halides, precipitating a silver halide and forming two different alkyl derivatives of nitrous acid having the same empirical formula. One of these isomers is an ester, the other a nitro body. The nitrogen is



attached directly to carbon in the nitro compound and to oxygen only in the ester :



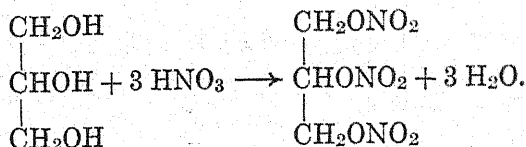
The ester, ethyl nitrite, is readily reduced to ethyl alcohol,  $\text{C}_2\text{H}_5\text{OH}$ , and hydroxylamine,  $\text{NH}_2\text{OH}$ , or to alcohol, water, and ammonia. Nitroethane, under the same treatment, is reduced to ethylamine,  $\text{C}_2\text{H}_5\text{NH}_2$ . Nitrogen attached to carbon is not removed in reduction processes at ordinary temperatures. Silver nitrite acts upon methyl iodide to form nitromethane,  $\text{CH}_3\text{NO}_2$ , almost free from the ester; but the higher alkyl halides yield mixed products. The isomers are readily separated by distillation, the nitro compound boiling at a higher temperature than the corresponding nitrite in every case. Nitromethane, for instance, boils at  $101.9^\circ$  and methyl nitrite at  $-12^\circ$ . The ethyl derivatives boil at  $114.8^\circ$  and  $17^\circ$  respectively. Each member of the high-boiling series can be reduced to an amine, indicating direct union between carbon and nitrogen; and each member of the low-boiling group can be hydrolyzed to an alcohol and nitrous acid, indicating that the nitrogen and carbon atoms are linked together through an oxygen atom.

**Nitric esters.** Esters of nitric acid are formed by the direct action of concentrated nitric acid on alcohols at  $0^\circ$  to  $40^\circ\text{C}$ . At higher temperatures the acid acts as an oxidizing agent. Nitric esters are combustible, and if heated under pressures greater than one atmosphere, they may explode. They boil at temperatures higher than the boiling points of the corresponding nitrites, as shown in the following table :

| ALKYL RADICAL<br>R      | NITRATE<br>R · O · NO <sub>2</sub> | NITRITE<br>R · O · NO | NITRO COMPOUND<br>R · NO <sub>2</sub> |
|-------------------------|------------------------------------|-----------------------|---------------------------------------|
| Methyl . . . . .        | + $65^\circ$ *                     | - $12^\circ$          | + $101.9^\circ$                       |
| Ethyl . . . . .         | $87.7^\circ$                       | + $17^\circ$          | $114.8^\circ$                         |
| Normal propyl . . . . . | $100.5^\circ$                      | $57^\circ$            | $131.5^\circ$                         |
| Isopropyl . . . . .     | $102^\circ$                        | $45^\circ$            | $120^\circ$                           |
| Normal butyl . . . . .  | $136^\circ$                        | $75^\circ$            | $151^\circ$                           |
| Isobutyl . . . . .      | $122.9^\circ$                      | $67^\circ$            | $140^\circ$                           |

\* Explodes.

*Nitroglycerine.* The most important ester of nitric acid is glyceryl trinitrate. Though commonly called nitroglycerine, it is not a true nitro body, for the nitrogen atom in the  $\text{NO}_2$  group is not attached to carbon. The compound is formed by injecting a spray of glycerol into a mixture of concentrated nitric and sulfuric acids which is agitated by compressed air:



The temperature of the mixture is held between  $20^\circ$  and  $30^\circ \text{C.}$ , and the time required for nitration is about one hour. The nitroglycerine floats on the waste acids. It is drawn off and washed with water and with dilute sodium carbonate solutions until free from acids.

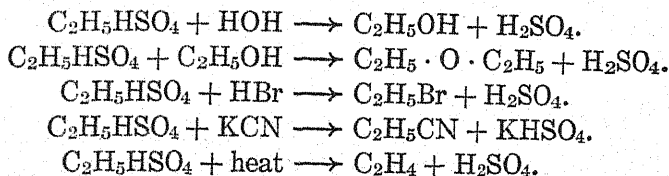
Nitroglycerine (m.p.  $8^\circ$ , sp. gr. 1.60) is a sweet, poisonous, oily liquid, colorless and odorless when pure but pale yellow as ordinarily prepared. It is practically insoluble in water; soluble in alcohol, benzene, and chloroform. It explodes when struck with a hammer or subjected to any other sudden shock. It is usually detonated by means of a mercury fulminate cap. The products of the explosion are carbon dioxide, water, nitrogen, oxygen, and nitrogen oxides. The energy released is equivalent to about six kilogrammeters per gram.

Dynamite is made by absorbing nitroglycerine in wood pulp or in infusorial earth. In this form the substance may be transported safely. Sodium nitrate, potassium nitrate, and sulfur are components of some brands of dynamite and blasting powders.

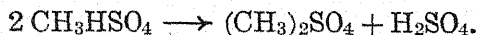
Blasting gelatins are made by absorbing nitroglycerine in nitrocellulose or in mixtures of nitrocellulose, wood pulp, and inorganic nitrates or chlorates. These are among the most powerful explosives known.

**Sulfuric esters.** Ethyl hydrogen sulfate,  $\text{C}_2\text{H}_5\text{HSO}_4$ , is an oily liquid (sp. gr. 1.316) which decomposes before boiling. It is formed from alcohol and concentrated sulfuric acid at  $100^\circ \text{C.}$  or from ethylene gas and fuming sulfuric acid. Its barium salt is soluble in water, a property that makes possible its separation from the unchanged acid. When heated with water, it regenerates the alcohol and acid. If heated with

alcohol, it produces sulfuric acid and ether. Alkyl halides and cyanides and many other types of compounds may be prepared by means of this reactive ester:



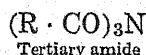
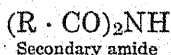
Methyl sulfate,  $(\text{CH}_3)_2\text{SO}_4$  (b.p.  $188^\circ$ , m.p.  $-31.8^\circ$ , sp. gr. 1.35), is frequently employed to introduce the methyl group into alcohols and amines. The hydrogen atoms in the groups OH,  $\text{NH}_2$ , and NH are replaced by methyl groups when treated with this ester. Sulfur trioxide acts on methyl alcohol at  $-5^\circ$  to  $0^\circ$ , producing methyl hydrogen sulfate. This product when distilled under reduced pressure yields the neutral ester:



Esters of halogen acids. The esters of hydrochloric, hydrobromic, and hydriodic acids have been discussed as alkyl halides.

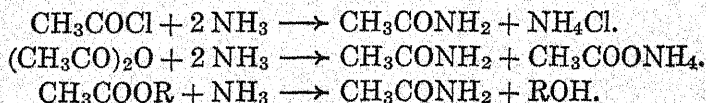
### ACID AMIDES

The acid amides are formed by replacing hydrogen of ammonia by acyl radicals. They are primary, secondary, or tertiary, depending upon the number of hydrogen atoms replaced.



The secondary and tertiary compounds are of little importance and quaternary amides are unknown. With the exception of formamide, a liquid, the primary compounds are colorless solids, soluble in water, and, when pure, they are odorless. The lower members can be distilled under atmospheric pressure without decomposition. They may be prepared from many acid derivatives.

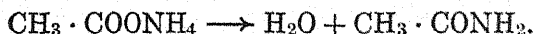
1. Amides are made by the action of ammonia on an acid chloride, an acid anhydride, or an ester:



The formation of acetamide, as indicated in the last equation, is accomplished by mixing ethyl acetate with twice its volume of a concentrated solution of ammonia and allowing the mixture to stand a few hours. The amide is isolated from the mixture by evaporating the water, alcohol, and excess of ammonia.

Ethyl acetate and acetamide are both susceptible to hydrolysis. Acetamide instead of ammonium acetate is obtained from a mixture of ethyl acetate, ammonia, and water because the reaction of the ester with ammonia (ammonolysis) is faster than the reaction with water (hydrolysis). The isolation of the amide depends also upon the fact that the hydrolysis of the amide is a slow reaction. If the mixture were allowed to stand for several days the products would be ammonium acetate and alcohol. Acetamide is purified by distillation. It boils at  $222^{\circ}$  and condenses to a colorless crystalline product which melts at  $81^{\circ}$ .

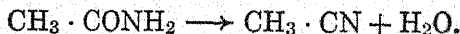
2. By heating the ammonium salt of an acid in a sealed tube at  $150^{\circ}$  to  $230^{\circ}$  for five or six hours an amide is produced:



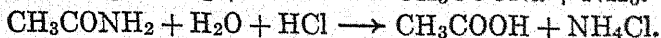
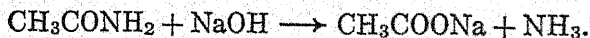
3. Amides are made by the union of water with nitriles:



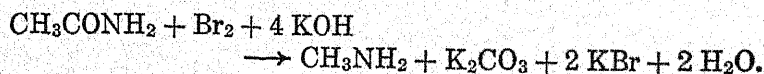
The addition is accomplished through the agency of hydrogen peroxide in alkaline solution. The reverse of this reaction occurs when an amide is heated with a dehydrating agent. Methyl cyanide is obtained when acetamide is heated with phosphorus pentoxide:



**Properties.** The amides are readily hydrolyzed by heating with water, the hydrolysis being catalyzed by hydrogen ions, and to a greater extent by hydroxide ions:

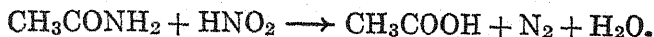


Amides are converted into amines through the agency of bromine and potassium hydroxide:



This reaction is especially successful with amides of low molecular weight (see page 431).

Amides react with nitrous acid, yielding nitrogen gas and the acid from which the amide was derived. The change is accomplished by warming the amide with a freshly prepared aqueous solution of sodium nitrite and hydrochloric acid:



## SOME MONOBASIC ACIDS AND DERIVATIVES

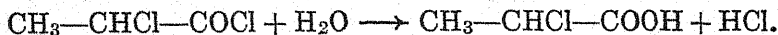
| ACID             |               |                  | ACID CHLORIDE |                  | ANHYDRIDE     |                  | AMIDE         |               |
|------------------|---------------|------------------|---------------|------------------|---------------|------------------|---------------|---------------|
|                  | Boiling Point | Specific Gravity | Boiling Point | Specific Gravity | Boiling Point | Specific Gravity | Boiling Point | Melting Point |
| Acetic . . . .   | 118.1°        | 1.049(20°)       | 52°           | 1.105(20°)       | 139.6°        | 1.078(21°)       | 222°          | 81°           |
| Propionic . .    | 141°          | 1.017(0°)        | 80°           | 1.065(20°)       | 166°          | 1.034(0°)        | 213°          | 79°           |
| Butyric (n) . .  | 163.5°        | 0.975(0°)        | 102°          | 1.028(20°)       | 198.2°        | 0.978(15°)       | 216°          | 116°          |
| Butyric (iso)    | 154.4°        | 0.965(0°)        | 92°           | 1.018(20°)       | 182°          | 0.958(16°)       | 220°          | 129°          |
| Valeric (n) . .  | 187°          | 0.956(0°)        | 128°          | 1.016(15°)       | 215°          | 0.929(20°)       | —             | 106°          |
| Valeric (iso)    | 176.7°        | 0.947(0°)        | 113°          | 0.989(20°)       | 215°          | 0.933(20°)       | 232°          | 137°          |
| Trimethylacetic  | 163.8°        | 0.905(50°)       | 106°          | —                | 190°          | —                | —             | 155°          |
| Caproic (n) . .  | 202.7°        | 0.945(0°)        | 153°          | —                | 243°          | 0.928(17°)       | 255°          | 98°           |
| Heptylic (n) . . | 223.5°        | 0.921(15°)       | 159.5°        | 0.959(20°)       | 258°          | 0.912(17°)       | 258°          | 96°           |
| Caprylic (n) . . | 237.5°        | 0.910(20°)       | 196°          | 0.973(8°)        | 285°          | —                | —             | 98°           |
| Palmitic (n) . . | 272° *        | 0.853(62°)       | 192° †        | —                | —             | —                | 236° †        | 106°          |
| Stearic (n) . .  | 291° *        | 0.847(69°)       | 215° †        | —                | —             | —                | 251° †        | 109°          |

## HALOGEN DERIVATIVES

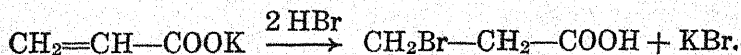
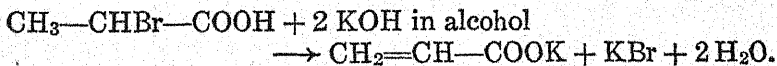
The acid chlorides, anhydrides, and esters form substitution products with chlorine and bromine. The halogen displaces hydrogen on the  $\alpha$ -carbon atom:



From the halogen-substituted compounds the  $\alpha$ -halogen acids are obtained by hydrolysis:



The  $\beta$ -halogen acids are obtained by indirect methods. Hot alcoholic potash converts an  $\alpha$ -halogen acid into a salt of an unsaturated acid. Treatment of the salt of the unsaturated acid with hydrobromic acid or hydriodic acid results in the formation of a  $\beta$ -halogen derivative of a saturated acid. (See page 387.)



\* At 100 mm.

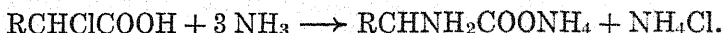
† At 15 mm.

‡ At 12 mm.

Chloroacetic acid,  $\text{CH}_2\text{ClCOOH}$ , is a colorless, crystalline solid which melts at  $63^\circ$  and boils at  $187^\circ$ . Dichloroacetic acid,  $\text{CHCl}_2\text{COOH}$  (b.p.  $191^\circ$ ), is a liquid at ordinary temperatures. Trichloroacetic acid,  $\text{CCl}_3\text{COOH}$ , melts at  $52^\circ$  and boils at  $195^\circ$ . These acids are stronger (more extensively ionized) than unsubstituted acetic acid. Their dissociation constants are listed on page 82.

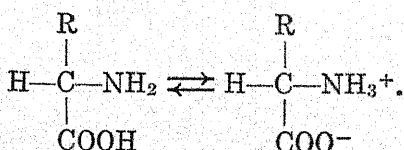
### AMINO ACIDS

The amino acids are derived from the saturated acids by several indirect methods. A concentrated aqueous solution of ammonia acts upon a halogen-substituted acid, converting it into the ammonium salt of an amino acid:



The best general methods for making amino acids involve the use of reagents that have not yet been described. Among these reagents are malonic ester and potassium phthalimide. Further discussion of the preparation of amino acids, therefore, will be postponed (see pages 294-419).

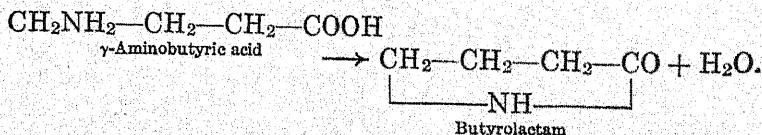
With few exceptions the  $\alpha$ -amino acids are colorless crystalline solids characterized by high melting points. Since they possess the basic amino group as well as the acidic carboxyl group, they exist largely in the form of intramolecular salts:



The  $\alpha$ -amino acids, when heated, yield cyclic anhydrides (see page 302). The  $\beta$ -amino acids are converted by heat into ammonium salts of unsaturated acids:



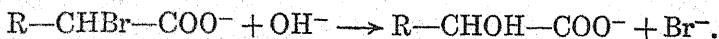
The  $\gamma$ -amino acids and  $\delta$ -amino acids yield lactams:



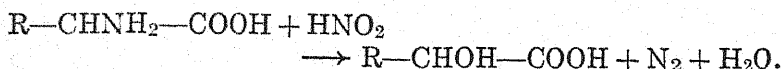
## HYDROXY ACIDS

Many hydroxy acids occur as constituents of plant and animal tissues. They possess the properties of alcohols as well as the properties of acids. They may be synthesized as follows:

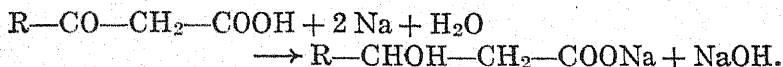
1. The halogen-substituted acids react with aqueous solutions of bases, forming salts of hydroxy acids:



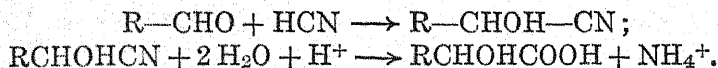
2. Amino acids are converted into hydroxy acids by treatment with nitrous acid:



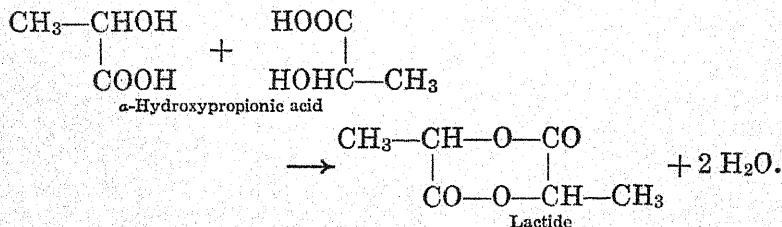
3. Aldehyde acids and ketone acids are reduced by sodium amalgam:



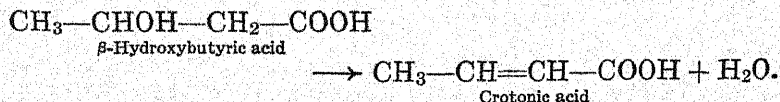
4. Aldehydes and ketones form addition products with hydrocyanic acid. These products — called cyanhydrins — are readily hydrolyzed to hydroxy acids:



Reactions of hydroxy acids. When heated the  $\alpha$ -hydroxy acids lose water, forming cyclic compounds:

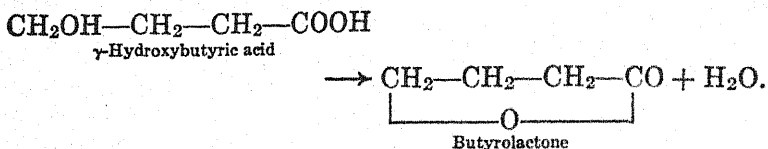


Under similar treatment  $\beta$ -hydroxy acids form unsaturated acids:

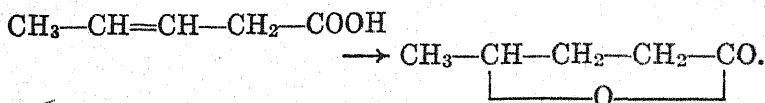




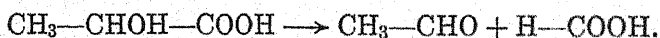
The  $\gamma$ -hydroxy acids and  $\delta$ -hydroxy acids are converted by heat into lactones:



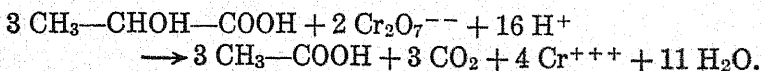
There are other methods for producing lactones, as, for example, by heating  $\beta\gamma$  or  $\gamma\delta$  unsaturated acids:



Lactic acid,  $\alpha$ -hydroxypropionic acid, is obtained from sour milk, or from the fermented juice of sugar beets. It is sold in the form of a sirupy liquid consisting of 85 per cent acid and 15 per cent water. The pure acid (obtained from an aqueous solution through vacuum distillation) boils at  $83^\circ$  under 1 mm. pressure. Some difficulty is experienced in making pure lactic acid, for it is very deliquescent and it decomposes rather easily when heated. Heat alone converts it into lactide, as indicated above, and when heated with sulfuric acid to  $130^\circ$  it yields acetaldehyde and formic acid:



Lactic acid is readily oxidized by chromic acid, the products being acetic acid, carbon dioxide, and water:



## OPTICAL ISOMERISM

Compounds having the same composition and the same molecular weight, but possessing different properties, are called *isomers*. In the earlier chapters we traced the origin of one type of isomerism to variations in molecular structure, and we called it *structural isomerism*. Thus, for example, we were able to account for differences in the properties of *n*-butane and *iso*-butane by assigning to the two molecules different structures. The former was represented by a continuous chain of carbon atoms and the latter by a branched chain. We found it possible to account for the properties of two propyl alcohols by placing the hydroxyl group on a terminal carbon atom in one formula and on the central carbon atom in the other.

In unsaturated compounds we found that a change in the position of the double or triple bond modifies the properties of a compound, and in connection with unsymmetrical derivatives of ethylene we encountered a type of isomerism due to different spacial arrangements of similar atoms or groups. This kind of structural variation we called *geometrical isomerism*. It is one type of stereoisomerism — an isomerism due to different arrangements of atoms or groups in space.

We must now consider a type of stereoisomerism, or space-isomerism, that is not dependent upon the presence of a double bond but that is due to an asymmetric structure, that is, a structure in which there is no plane of symmetry. Quartz crystals and tartaric acid crystals are asymmetric solids. Asymmetric molecules are formed whenever four dissimilar atoms or groups become attached to the same atom, and substances composed of asymmetric molecules exist in isomeric forms not only in crystalline state but also in the liquid and gaseous states. Isomers of this type can be distinguished from each other by observing their effects upon plane-polarized light. They possess different optical properties, and they are classified as *optical isomers*.

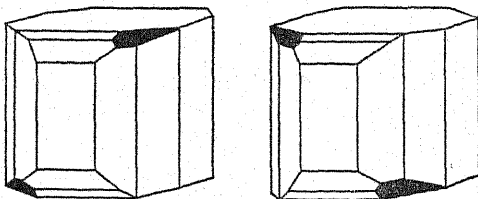
Light is polarized when it passes through a *Nicol prism* — a prism made of crystalline tourmaline or Iceland spar. The

light, before entering the prism, is the result of wave motions in all planes that are perpendicular to the path of propagation of the beam. The light that gets through the prism is plane-polarized; that is to say, the vibrations are in a single plane. The ray of light that passes through one Nicol prism will pass through a second similar prism if the two are held in corresponding positions; but if the second prism be slowly turned while the faces of the two are kept parallel to each other, the light emerging from the second prism gradually diminishes in intensity. Total darkness is produced when the second prism has been rotated through an angle of  $90^\circ$ .

In 1815 Biot observed that if a transparent layer of quartz crystal be placed between two tourmaline plates, then the maximum illumination is obtained not when the tourmaline plates are in corresponding positions but after one of them has been turned through an angle, the magnitude of which depends upon the thickness of the quartz. In other words, light is polarized when it passes through a layer of tourmaline, but the plane of polarization is changed when this light passes through a layer of quartz. Some of Biot's quartz crystals were *dextro-rotatory* (turned the plane of polarization to the right) and others were *lævorotatory* (rotated the plane of polarization to the left). Biot discovered also that solutions of many organic compounds have the same effect. By passing plane-polarized light through tubes that contained solutions of sugars, salts, and organic acids, he found that some of them were optically active (that is, they turned the plane of polarization either to the right or to the left) but that most of them were optically inactive. He discovered that the rotation produced by a solution of an optically active compound is proportional to its concentration and proportional also to the length of the column of solution which the light traverses. The exact angle of rotation is dependent also upon the wave length of the light used.

In 1848 Pasteur, familiar with Biot's work, and knowing that quartz crystallizes in hemihedral forms, reached the conclusion that optical activity might have a definite relationship to crystal form. He tried to confirm this idea by making a careful study of tartaric acid crystals. Three tartaric acids were known at that time, a dextrorotatory acid, a lævorotatory acid, and an optically inactive acid. Pasteur observed that the optically active tartaric acids and their salts form hemihedral crystals,

and he supposed that the inactive tartaric acid, or a salt of this acid, would form symmetrical crystals. The result of his investigation was at first disappointing, for he found that inactive tartaric acid, like the optically active acids, yielded hemihedral crystals. His very careful examination of the crystals of a salt of the inactive acid, however, revealed the fact that they were not all exactly alike. The angles between the faces were identical in all of them, but the crystals were not symmetrical and some of them were mirror images of others. He could pick out right-hand and left-hand crystals, and with the aid of a magnifying glass and a pair of tweezers he did this until he had a supply of both kinds. He dissolved the two types of crystals separately

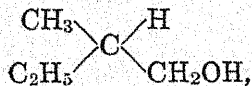


Crystal forms of sodium ammonium *d*-tartrate and sodium ammonium *l*-tartrate

and examined the solutions with the aid of a polariscope. One solution was dextrorotatory and the other was laevorotatory. A mixture of equal quantities of the two solutions was optically inactive.

In 1873 Wislicenus published the results of his study of the lactic acids, which differ only in their effects upon polarized light, and he made the suggestion that "if it is once granted that molecules can be structurally identical and yet possess dissimilar properties, it can only be explained on the ground that the difference is due to a different arrangement of their atoms in space."

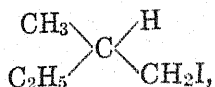
With the works of Pasteur and Wislicenus as a background, van't Hoff and Le Bel independently and simultaneously extended the structure theory to cover all cases of optical isomerism. They pointed out the fact that the compounds then known to exhibit optical activity each had at least one carbon atom attached to four different atoms or groups. Thus, for example, in the optically active amyl alcohol called secondary butyl carbinol,\*



\* This amyl alcohol is a primary alcohol. The name "secondary butyl" refers to the radical,  $(\text{CH}_3)(\text{C}_2\text{H}_5)\text{CH}-$ , which is substituted for one hydrogen atom in carbinol,  $\text{CH}_3\text{O}^\text{H}$ .

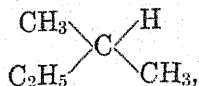
the central carbon atom is attached to four different radicals, namely,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{H}$ , and  $\text{CH}_2\text{OH}$ .

With phosphorus and iodine this alcohol is converted into an iodide,



which is asymmetric and optically active.

The iodide, in turn, may be reduced to the hydrocarbon



which is no longer asymmetric, and the compound is optically inactive.

Three-dimensional models should be used to clarify the structural relationship that exists between optical isomers. Insert four short pieces of wire into a ball or a cork so that the wires extend outward at tetrahedral angles from the center. Attach to each of the four wires a small ball and let these four small balls be colored differently to represent four different atoms. Make another model of exactly the same kind. Place the two models side by side and arrange the balls of corresponding colors so that they occupy similar positions in space. Now, change the positions of two of the balls on one model, leaving the other as originally constructed. It is now impossible to place the models in such positions that they coincide throughout. It is possible, however, to place them in such positions that one corresponds to a mirror reflection of the other.

When plane-polarized light enters an optically active substance — a substance possessing no plane of symmetry — the plane of polarization is turned to the right or to the left and the farther the light travels through such a medium the greater the angle through which the plane of polarization is rotated. A polariscope is used to measure the extent of this rotation. The instrument is equipped with two Nicol prisms, one of which can be rotated. A tube filled with the liquid or solution to be examined is inserted between the two prisms. One of the prisms is then rotated until the illuminated field appears as it did before the tube was inserted. The angle of rotation is read from a scale.\*

\* The actual rotation is proportional to the concentration of the solution and to the length of the tube.

The specific rotation of a compound,  $[\alpha]_D$ , is the angle of rotation of plane-polarized light of wave length corresponding to the yellow sodium line in the solar spectrum when it traverses 10 cm. of a solution of the compound at  $20^\circ \text{C}$ ., the con-

A mixture of equal quantities of *dextro* and *laevo* forms of a compound has no effect on polarized light. Such a mixture is said to be *racemic*. We frequently use the prefix *d*-, *l*-, or *r*- in connection with the name of a compound to show that it is dextrorotatory, levorotatory, or racemic. A racemic mixture of optically active forms is sometimes regarded as a third substance having the same structural formula.

One asymmetric carbon atom in a molecule gives rise to two optically active forms and one inactive (racemic) mixture of the two. More stereoisomers are possible if the compound has two or more asymmetric atoms.\*

**Resolution of racemic mixtures.** Three general methods are employed to resolve racemic mixtures into their optically active components.

1. Some microorganisms grow in racemic mixtures, destroying one isomer and leaving the other form unchanged. With the aid of *Penicillium glaucum*, Pasteur obtained levotartaric acid from racemic tartaric acid. The dextrorotatory form was removed by the organism.

2. In a few instances the two forms differ in crystalline structure, and may be separated by mechanical means. Quartz and the sodium ammonium salt of racemic tartaric acid produce crystals some of which have right and others left hemihedral faces.

centration of the solution being one gram of the solute per cubic centimeter of solution. Such a concentration cannot ordinarily be obtained, but the theoretical rotation under such conditions may be calculated from observations of the rotation produced in any solution of known concentration.

$$[\alpha]_D = \frac{av}{lw}$$

In this equation  $[\alpha]_D$  is the specific rotation of the compound,  $a$  is the observed rotation (deg.),  $v$  the volume of the solution (cc.),  $l$  the length of the column (dm.), and  $w$  the weight of the dissolved substance (grams). For optically active liquids,

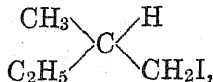
$$[\alpha]_D = \frac{a}{ld}$$

In this case  $d$  is the density of the liquid  $\left(\frac{\text{g.}}{\text{cc.}}\right)$ .

\* Let  $n$  represent the number of asymmetric carbon atoms in a molecule,  $a$  the number of optically active forms,  $c$  the forms that are inactive owing to internal compensation, and  $r$  the racemic forms; then (1) if the molecule cannot be divided into similar halves,  $a = 2^n$ ;  $c = 0$ ; (2) if  $n$  is even and the molecule forms similar halves,  $a = 2^{n-1}$ ;  $c = 2^{\frac{n-1}{2}}$ ; (3) if  $n$  is odd and the formula yields similar halves by excluding the middle carbon atom,  $a = 2^{n-1} - 2^{\frac{n-1}{2}}$ ;  $c = 2^{\frac{n-1}{2}}$ . ( $r$  always equals  $\frac{a}{2}$ .)

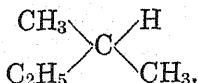
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2. In a few instances the two forms differ in crystalline structure, and may be separated by mechanical means. Quartz and the sodium ammonium salt of racemic tartaric acid produce crystals some of which have right and others left hemihedral faces.

centration of the solution being one gram of the solute per cubic centimeter of solution. Such a concentration cannot ordinarily be obtained, but the theoretical rotation under such conditions may be calculated from observations of the rotation produced in any solution of known concentration.

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$$[\alpha]_D = \frac{a}{l d}$$

In this case  $d$  is the density of the liquid  $\left(\frac{\text{g.}}{\text{cc.}}\right)$ .

\* Let  $n$  represent the number of asymmetric carbon atoms in a molecule,  $a$  the number of optically active forms,  $c$  the forms that are inactive owing to internal compensation, and  $r$  the racemic forms; then (1) if the molecule cannot be divided into similar halves,  $a = 2^n$ ;  $c = 0$ ; (2) if  $n$  is even and the molecule forms similar halves,  $a = 2^{n-1}$ ;  $c = 2^{\frac{n}{2}-1}$ ; (3) if  $n$  is odd and the formula yields similar halves by excluding the middle carbon atom,  $a = 2^{n-1} - 2^{\frac{n-1}{2}-1}$ ;  $c = 2^{\frac{n-1}{2}-1}$ . ( $r$  always equals  $\frac{a}{2}$ .)

3. The best method from the standpoint of general application consists in forming condensation products with other optically active compounds. A racemic mixture forms two different derivatives with the same optically active reagent, and these derivatives may be separated by taking advantage of their differences in solubilities, boiling points, and so on. Such derivatives are not optical isomers and hence they have different chemical and physical properties. Suppose, for example, we have a racemic acid composed of components  $A^+$  and  $A^-$ . If we treat the mixture with a levorotatory base,  $B^-$ , two different salts will be formed,  $A^+B^-$  and  $A^-B^-$ . These may be separated by fractional crystallization and subsequently decomposed to yield the free acids  $A^+$  and  $A^-$ . The resolution of a racemic acid may usually be accomplished with the aid of the optically active bases brucine, strychnine, quinine, and cinchonine. *d*-Tartaric acid, *d*-bromocamphor sulfonic acid, or *l*-malic acid may be used to separate optically active bases. Methods have been devised for separating optically active compounds that are neither acidic nor basic.\*

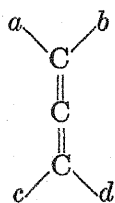
**Asymmetric syntheses.** Attempts to prepare optically active compounds by synthetic methods without the aid of optically active reagents have failed. It is an easy matter to synthesize compounds having asymmetric carbon atoms, but there is always as much probability of obtaining one as the other of the active forms. As a result of this condition the two forms are produced in equal amounts and the synthetic product is racemic. Thus in the reduction of acetophenone,  $CH_3 \cdot CO \cdot C_6H_5$ , to  $CH_3 \cdot CHOH \cdot C_6H_5$ , the central carbon atom is rendered asymmetric, but there is no way to control the reaction so that one form will predominate in the mixture.

If, on the other hand, a new carbon atom is rendered asymmetric in a molecule which is already asymmetric and optically active, there may be a definite orientation of the entering groups favoring the formation of one of the optical isomers. This occurs in some reactions of *d*-glucose. The carbon atom of the aldehyde group is rendered asymmetric by addition of HCN, but the two stereoisomeric cyanhydrins are not formed in equal amounts.†

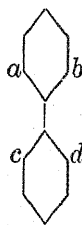
\* For details relating to the resolution of methyl-hexyl carbinol see "Organic Syntheses," Vol. 6, p. 68. John Wiley and Sons, 1926.

† For a critical review of the literature in this field see P. D. Ritchie's "Asymmetric Synthesis and Asymmetric Induction." Oxford University Press, 1933.

It is possible to establish asymmetry in a molecule by other means than the attachment of four different atoms or groups to a carbon, nitrogen, silicon, or other multivalent atom. Optically active compounds of the following types have been prepared:



I!



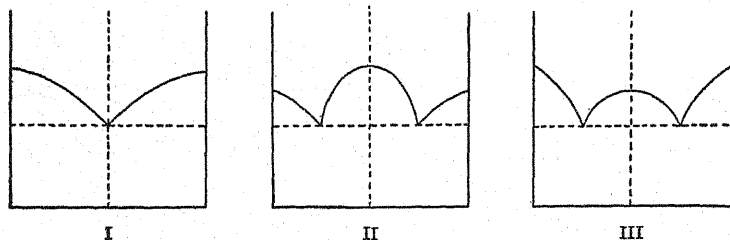
II

The double-bond system in I keeps the atoms or groups *a* and *b* in a plane at right angles to the plane of the groups *c* and *d*. There is, therefore, no plane of symmetry in the molecule as a whole. In type II the ortho substituents are close enough together to prevent free and independent rotations of the two rings. The two ends of the molecule are forced to maintain relatively fixed positions with the carbon atoms of the two rings not in the same plane. Rotation is sufficiently curtailed to permit the isolation of stereoisomeric forms of such compounds.\*

**Racemization.** Many optically active compounds may be converted into racemic mixtures by heating them alone or with acids or alkalis. Dextrotartaric acid is racemized by heating it with a little water in a sealed tube for five or six hours at 175°, or by boiling it with a concentrated solution of sodium hydroxide. The reaction takes place in two stages, mesotartaric acid being formed by rearrangement of two of the groups on one carbon atom, and the lævorotatory compound by a similar rearrangement involving both asymmetric atoms. This accounts for the fact that mesotartaric acid predominates in the early stages of the process, whereas racemic acid constitutes the final product. In many compounds having two or more asymmetric carbon atoms, the optically active forms are only partially racemized — the configuration with respect to one or more of the asymmetric groups remaining undisturbed. The interesting phenomenon of obtaining a reversal in the sign of optical rotation is discussed under the Walden inversion.

\* Searle and Adams, *J. Am. Chem. Soc.*, 56, 2112 (1934). Patterson and Adams, *J. Am. Chem. Soc.*, 57, 762 (1935).

In some cases a racemic product is not merely a mixture of the optically active forms but a compound of the two. Melting-point determinations and other applications of the phase rule may be made to distinguish between the two states. Although optical isomers melt at the same temperature, mixtures of the two melt at a lower temperature, the minimum temperature corresponding to an equimolecular mixture — the racemic product. If the



stereoisomers do not react with each other to form a definite compound, the melting-point curve produced by the addition of one active form to the other is represented in I. If the two forms produce a racemic compound, melting at a higher temperature than that of the components, the melting-point curve belongs to the type shown in II, and if it melts at a lower temperature than the melting point of the optically active forms, the curve corresponds to III. In any case of compound formation, the melting point of the pure compound is higher than that of a mixture of the compound with a small amount of either active form.

The addition of a small amount of one of the active modifications to the racemic product, therefore, elevates the melting point if the inactive substance is a mixture and lowers the melting point if the product is a compound.

## POLYBASIC ACIDS AND THEIR DERIVATIVES

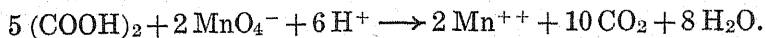
Acids having two or more carboxyl groups in the molecule are produced by reactions analogous to those used for the synthesis of monobasic acids. The hydrolysis of compounds having more than one cyanide radical, the oxidation of alcohols having more than one  $-\text{CH}_2\text{OH}$  group, and the oxidation of dialdehydes are methods of general application. The important members of this series are the dibasic acids derived from normal (straight-chain) hydrocarbons with the two carboxyl groups attached to the terminal carbon atoms.

They are colorless, crystalline solids. The compounds having an odd number of carbon atoms are more soluble in water and melt at lower temperatures than those having approximately the same molecular weights but containing an even number of carbon atoms.

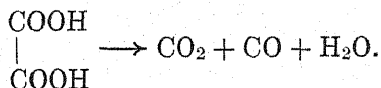
| NAME OF ACID       | FORMULA                                 | MELTING POINT | SOLUBILITY IN 100 G. WATER, 20° |
|--------------------|---|---------------|---------------------------------|
| Oxalic . . . . .   | $\text{COOH}-\text{COOH}$               | 189°          | 8.6                             |
| Malonic . . . . .  | $\text{COOH}-\text{CH}_2-\text{COOH}$   | 135.6°        | 73.5                            |
| Succinic . . . . . | $\text{COOH}(\text{CH}_2)_2\text{COOH}$ | 185°          | 5.8                             |
| Glutaric . . . . . | $\text{COOH}(\text{CH}_2)_3\text{COOH}$ | 97.5°         | 63.9                            |
| Adipic . . . . .   | $\text{COOH}(\text{CH}_2)_4\text{COOH}$ | 151°          | 1.5                             |
| Pimelic . . . . .  | $\text{COOH}(\text{CH}_2)_5\text{COOH}$ | 103°          | 5                               |
| Suberic . . . . .  | $\text{COOH}(\text{CH}_2)_6\text{COOH}$ | 140°          | 0.16                            |
| Azelaic . . . . .  | $\text{COOH}(\text{CH}_2)_7\text{COOH}$ | 106.5°        | 0.24                            |
| Sebacic . . . . .  | $\text{COOH}(\text{CH}_2)_8\text{COOH}$ | 127°          | 0.10                            |

Oxalic acid,  $\text{C}_2\text{H}_2\text{O}_4 \cdot 2 \text{H}_2\text{O}$ , is widely distributed in nature. In the form of its salts it occurs in many plants, especially in the oxalis family. Rhubarb contains a sufficient quantity to arrest the growth of organisms that cause decay, and the plant can be preserved for weeks by immersion in water without artificial sterilization. The acid is used in the manufacture of some dyes, and as a mordant in calico printing. It is the chief source of formic acid.

Oxalic acid crystallizes with two molecules of water, and in this form it is weighed for standardizing permanganate solutions for use in volumetric analysis. The reaction in acid solution is represented as follows:

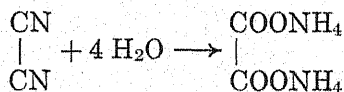


The hydrated acid loses water and sublimes at  $150^\circ$ , with partial decomposition. When heated with concentrated sulfuric acid, it decomposes in the same way, yielding carbon dioxide, carbon monoxide, and water, or carbon dioxide and formic acid:

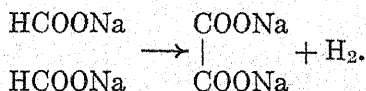


Oxalic acid is stable in the presence of some oxidizing agents, — for example, concentrated nitric acid. It is made commercially by oxidizing starch or cellulose with concentrated nitric acid or by heating sawdust to  $250^\circ$  with a concentrated solution of sodium hydroxide.

It can be synthesized by the hydrolysis of cyanogen:



or by rapidly heating sodium formate:



The last reaction is especially interesting, for it reveals a genetic relationship between oxalic and formic acids, the first members of the two most important series of the saturated acids. The preparation of formic acid from oxalic acid has been mentioned (p. 86). To obtain free oxalic acid from the soluble ammonium and sodium salts formed in the reactions shown above, lime is added to precipitate the insoluble calcium oxalate,  $\text{Ca}(\text{C}_2\text{O}_4)_2$ . The calcium salt is then decomposed with sulfuric acid, and the liberated oxalic acid is extracted with water, from which it crystallizes when the solution is concentrated by evaporation.

*Malonic acid* is a compound of prime importance on account of the many syntheses that can be made with the aid of its derivatives. It is made from acetic acid by a series of reactions that establish the constitution of the molecule. Chlorine acts upon acetic acid, producing a white crystalline derivative, chloroacetic acid, having the formula  $\text{ClCH}_2\text{COOH}$ .\* Potassium cyanide reacts with chloroacetic acid, as it does with alkyl halides, forming potassium chloride and leaving the cyanide radical attached to carbon. Cyanoacetic acid, therefore, has the structure  $\text{CN} \cdot \text{CH}_2 \cdot \text{COOH}$ . The cyanide radical is always susceptible to hydrolysis, being thereby converted into the carboxyl group. Malonic acid is produced from cyanoacetic acid by boiling it with a solution of sulfuric acid. Its structure, therefore, is  $\text{COOH} \cdot \text{CH}_2 \cdot \text{COOH}$ .

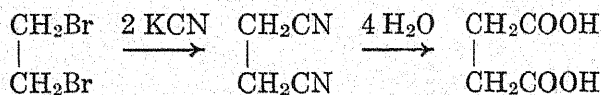
When malonic acid is heated above its melting point, it decomposes into acetic acid and carbon dioxide:



This is an example of a general reaction. When a compound having two carboxyl groups attached to the same carbon atom is heated above its melting point, it yields carbon dioxide and leaves hydrogen in the place of one carboxyl group.

When heated with phosphorus pentoxide, malonic acid yields carbon suboxide and water as well as carbon dioxide and acetic acid.

*Succinic acid*,  $\text{COOH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COOH}$  (m.p.  $185^\circ$ , b.p.  $235^\circ$ ), occurs in amber, from which it may be obtained by distillation. It is formed in small amounts as a by-product when alcohol is made by the fermentation of glucose. It is made from ethylene dibromide by a process that establishes its structure:

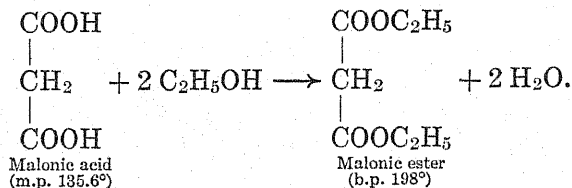


\*The reaction between chlorine and pure acetic acid is extremely slow. The practical procedure is to pass chlorine gas into a mixture of acetic acid and red phosphorus. Part of the acetyl chloride, which is first formed, reacts with acetic acid, forming acetic anhydride. Chlorine readily replaces hydrogen on the  $\alpha$ -carbon atom in either the acid chloride or the anhydride, and from either of these derivatives chloroacetic acid is obtained by hydrolysis.

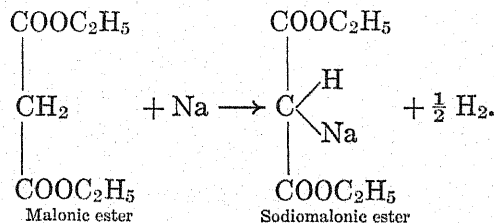


## ESTERS OF DIBASIC ACIDS

*Malonic ester.* When a mixture of malonic acid and absolute ethyl alcohol is saturated with hydrogen chloride gas and warmed, an ester is formed:

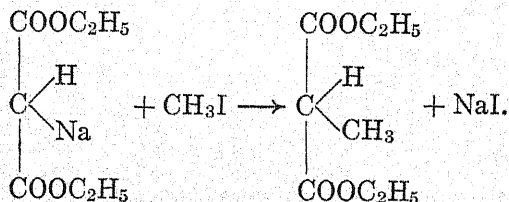


The hydrogen atoms of the methylene group in malonic ester are replaceable by sodium or potassium or by chlorine or bromine. When metallic sodium is dissolved in malonic ester, hydrogen is evolved and a solid sodium derivative of the ester is formed. The reaction is usually written as follows:

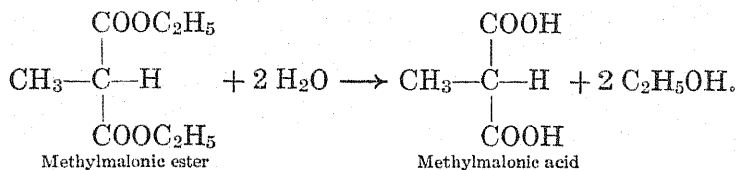


Sodiomalonic ester may be formed also by adding sodium ethylate to an alcoholic solution of malonic ester. In this case no hydrogen is evolved. The formula for sodiomalonic ester showing the sodium atom attached directly to carbon is probably incorrect, but it may be written in this form for the present purpose. Evidence relating to the structure of the compound will be presented in a later chapter.

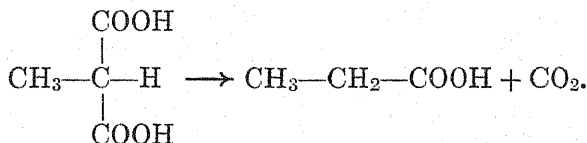
Sodiomalonic ester reacts readily with an alkyl halide, forming an alkyl-substituted malonic ester and a sodium halide:



On hydrolysis this ester yields methylmalonic acid :

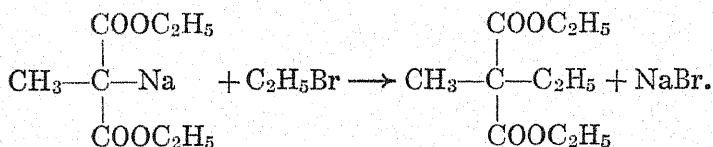


Methylmalonic acid, having two carboxyl groups attached to the same carbon atom, may be decomposed by heat. The products of this decomposition are carbon dioxide and propionic acid:

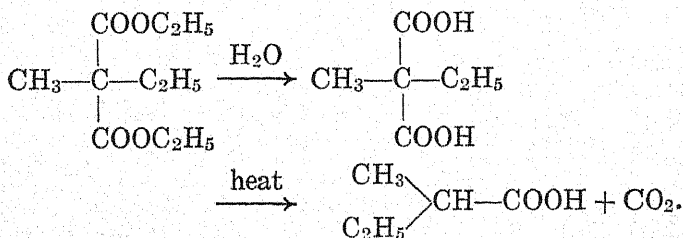


This constitutes a synthesis of propionic acid from malonic ester. Any alkyl radical may be substituted for hydrogen in malonic ester, and therefore any homologue of acetic acid may be prepared from this ester.

The remaining methylene hydrogen in an alkylmalonic ester may be replaced by sodium, and this, in turn, will react with an alkyl halide. The sodium derivative of methylmalonic ester reacts with ethyl bromide as follows:

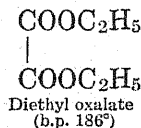
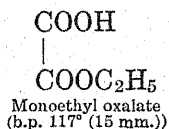
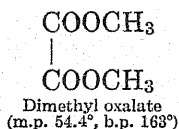


When hydrolyzed this yields methylethylmalonic acid. The latter is decomposed by heat into carbon dioxide and methylethyl acetic acid or 2-methyl-butaneic acid.



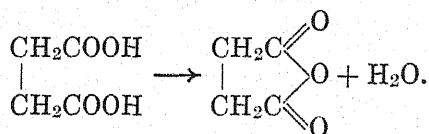
Other applications of this reaction will be considered later.

Esters of other dicarboxylic acids are readily obtained by applying the general method of synthesis outlined in connection with malonic ester. The acid is heated with an alcohol in the presence of hydrogen chloride or a little sulfuric acid. One or both of the carboxyl groups may be esterified. The formulas of some esters of oxalic acid are shown below:



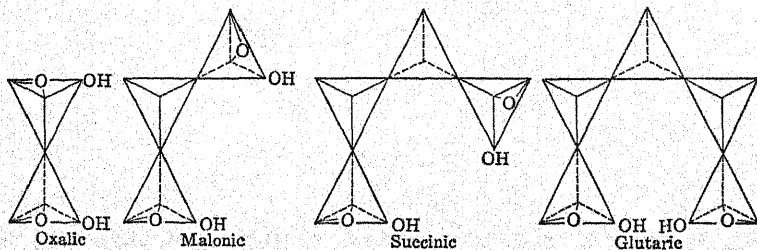
### ACID ANHYDRIDES

Succinic acid loses water when heated with sulfuric acid or phosphorus oxychloride, forming succinic anhydride:



Isosuccinic acid,  $\text{CH}_3 \cdot \text{CH} \begin{array}{l} \nearrow \text{COOH} \\ \searrow \text{COOH} \end{array}$ , does not form an anhydride, but decomposes when heated above its melting point ( $130^\circ$ ) into carbon dioxide and propionic acid.

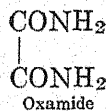
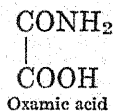
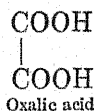
Oxalic and malonic acids do not form true anhydrides, while succinic and glutaric acids form them readily. This fact is explained by a consideration of the three-dimensional figures formed by molecules made up of chains of two or more carbon atoms. Assuming, once more, that the carbon atom is a regular tetrahedron with its valence electrons stationed at the four apices, the acids mentioned may be represented graphically as follows:



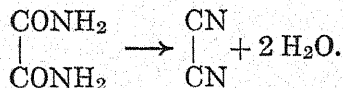
It will be observed that the hydroxyl groups that are involved in the anhydride formation approach each other as the number of carbon atoms increases from two to five. To link the first and fourth carbon atoms through oxygen by eliminating water involves less strain in the molecule than would be required to connect the first and second or the first and third carbon atoms. In consequence of this close approach of the hydroxyl groups, succinic acid can form an anhydride whereas oxalic and malonic acids cannot. The same sort of reasoning leads to the conclusion that glutaric acid should form an anhydride even more readily than does succinic, which is actually the case. Acids of this series having five or more carbon atoms may form anhydrides without strain. The higher members, however, do not readily yield anhydrides, for the rate of reaction between the carboxyl groups decreases as the length of the chain increases.

### AMIDES OF DIBASIC ACIDS

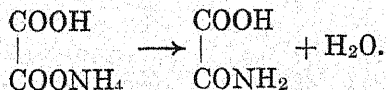
One or both of the carboxyl groups in a dibasic acid may be involved in amide formation. Compounds containing one unchanged carboxyl group and one  $\text{CONH}_2$  group are called amic acids.



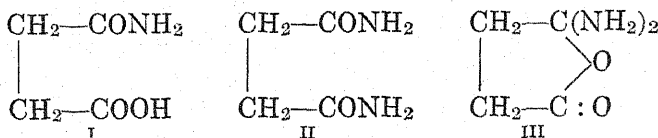
Oxamide is a white, crystalline substance which is sparingly soluble in water. At  $180^\circ$  it sublimes with partial decomposition. Cyanogen and water are the principal decomposition products:



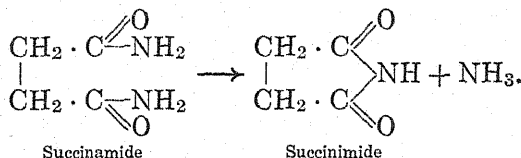
The diamides are formed by reactions analogous to those used for amides of monobasic acids. Diethyl oxalate, for instance, when warmed with ammonia, yields oxamide. Acid ammonium oxalate, when heated, yields the white crystalline oxamic acid:



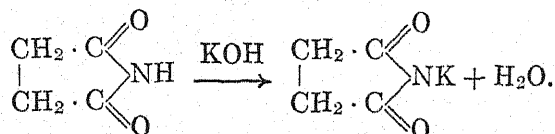
Succinic acid yields a monoamide, succinamic acid (I), and two diamides (II and III) :



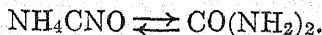
When heated the diamide represented by formula II yields ammonia and succinimide :



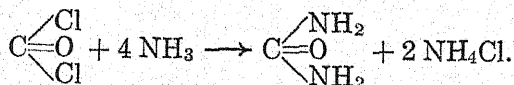
Succinimide (m.p. 126°, b.p. 288°) crystallizes with one molecule of water. It is neutral to litmus, but reacts with alcoholic potash, forming a salt :



*Urea.* The diamide of carbonic acid, urea, was the first organic compound to be prepared by an artificial method. The synthesis was accomplished through the reversible conversion of ammonium cyanate into urea, a reaction first observed by Wohler (1828). The change occurs during the evaporation of an aqueous solution of ammonium cyanate :



Urea may be prepared by the action of ammonia on phosgene gas :



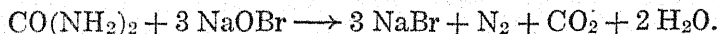
It crystallizes in colorless prisms, melting at 132°, and dissolves readily in water and in alcohol.

Urea constitutes from 2 to 5 per cent of the urine. The average amount excreted daily by an adult person is between 25 g. and 35 g. It is formed along with smaller quantities of uric acid, creatine, ammonia, and other nitrogen compounds as an oxidation product of the proteins in the living tissues. It may be obtained from urine by evaporation and extraction of the residue with hot alcohol, or in a more pure state by concentrating the sample through partial evaporation and acidifying with nitric acid. The slightly soluble urea nitrate,  $\text{CO}(\text{NH}_2)_2\text{HNO}_3$ , precipitates. The salt is decomposed by barium carbonate, and the urea is separated from the resulting barium nitrate by extraction with alcohol. Oxalic acid also forms an insoluble salt of urea.

When heated above its melting point, urea decomposes, with the liberation of ammonia and the production of cyanuric acid and biuret.

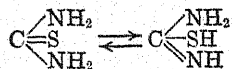
An alkaline solution of biuret,  $\text{NH}_2 \cdot \text{CO} \cdot \text{NH} \cdot \text{CO} \cdot \text{NH}_2$ , acquires a violet color when a solution of a copper salt is added. This is known as the biuret test and is mentioned in connection with the color reactions of the proteins.

The quantitative estimation of urea is accomplished by measuring the nitrogen evolved from a weighed sample when treated with an alkaline solution of sodium hypobromite:



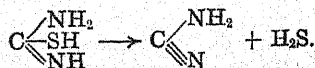
This reaction was used for many years as a basis for the clinical estimation of urea in urine. It is, however, entirely untrustworthy in this connection, for other nitrogen compounds sometimes found in urine respond to the test.

Thiourea, the diamide of thiocarbonic acid, exists in two forms, which, in solution, establish a tautomeric equilibrium:

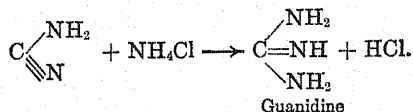


The free amide in the solid state is known only as colorless crystals (m.p.  $172^\circ$ ), soluble in water and insoluble in alcohol, but many of its derivatives have been isolated in isomeric forms.

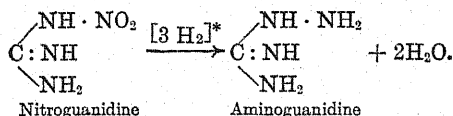
When warmed with mercuric oxide, thiourea yields cyanamide:



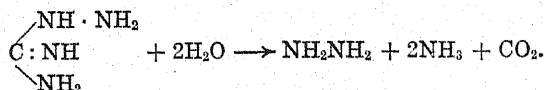
Guanidine, a colorless, crystalline, basic compound, is closely related to urea and thiourea. It may be prepared from cyanamide and an ammonium salt:



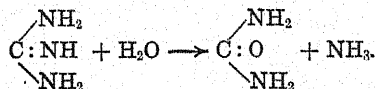
The hydrochloric acid is not liberated, but combines with the guanidine to form a salt. With concentrated nitric acid guanidine forms a nitro compound, and like any other nitro body this compound can be reduced to an amine of corresponding structure:



Aminoguanidine undergoes hydrolysis in either acid or alkaline solution, the products being hydrazine, ammonia, and carbon dioxide:



Guanidine also is readily hydrolyzed in alkaline solution, the products being urea and ammonia:



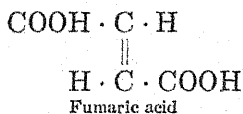
### UNSATURATED ACIDS

*Fumaric acid* and *maleic acid* are unsaturated compounds corresponding to the formula  $\text{C}_4\text{H}_4\text{O}_4$ . Fumaric acid sublimates at  $200^\circ$ . It is found in small quantities in many plants. It is not very soluble in water (1 : 160). Maleic acid is not found in nature. It is a synthetic product only. It melts at  $130^\circ$  and dissolves in less than twice its weight of water at  $15^\circ$ .

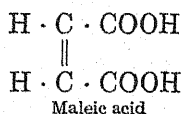
When heated, maleic acid yields an anhydride, one molecule of water being eliminated. Fumaric acid does not form an anhydride.

\* The reduction is actually accomplished by treatment with titanous chloride or through the agency of tin and hydrochloric acid. Equations representing oxidation and reduction processes are sometimes balanced by using the symbols for free oxygen or free hydrogen even in cases where these gases fail to accomplish the indicated results. When used in connection with reactions that actually require other reagents the symbols for hydrogen and oxygen are placed within brackets.

Fumaric and maleic acids are both obtained from malic acid,  $\text{COOH} \cdot \text{CHOH} \cdot \text{CH}_2 \cdot \text{COOH}$ , by eliminating one molecule of water, which is accomplished by heat alone. At  $140^\circ$  fumaric acid is formed; at  $200^\circ$  maleic anhydride is the chief product. Both acids have the structural formula  $\text{COOH} \cdot \text{CH} : \text{CH} \cdot \text{COOH}$ . They are geometrical isomers having the following structures:

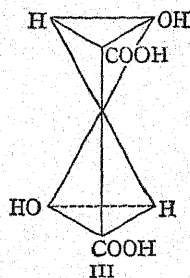
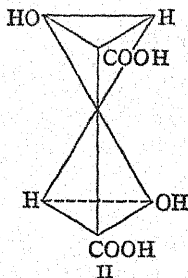
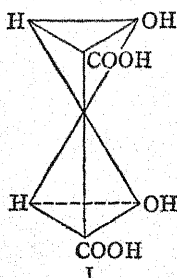


and

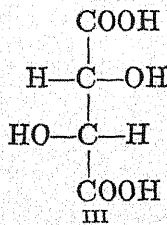
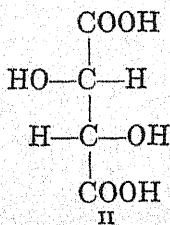
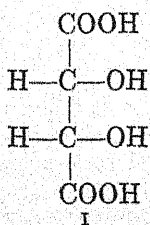


### HYDROXY ACIDS

*Tartaric acids.* There are four tartaric acids corresponding to the formula  $\text{COOH} \cdot \text{CHOH} \cdot \text{CHOH} \cdot \text{COOH}$ . They present an interesting case of stereoisomerism. The phenomenon of optical activity was considered in connection with the amyl alcohols (p. 115), and the cause was traced to an asymmetric structure of the molecule. Two of the tartaric acids are optically active and two inactive. Three structural formulas for tartaric acids may be represented graphically as follows:



Imagine these tetrahedra flattened out on the plane of the paper; then the same configurations are represented by the simple projection formulas:

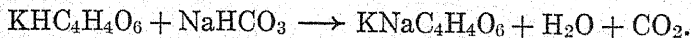




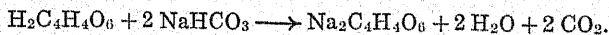
One of the inactive tartaric acids is a racemic compound consisting of a mixture of equal quantities of the mirror images represented by formulas II and III. The other inactive acid cannot be resolved into optically active forms and must correspond to a single formula. It is not a mixture. If formula I were cut in two between the asymmetric atoms, and if the lower half were rotated in the plane of the paper through an angle of  $180^\circ$ , the lower half would appear as the mirror image of the upper half. If either of the other structures were severed and rotated in the same manner, the two halves would appear to be identical. In a structure of the type represented by formula II or III any effect the upper half of the molecule has on polarized light is duplicated by the lower half; but in a structure like formula I, if the upper half tends to turn the plane of polarization to the right, the lower half rotates it to the left, and since the two ends are similarly asymmetric, that is, identical groups are attached to both asymmetric carbon atoms, the gyrotory power of one is exactly counterbalanced by the other. Such a molecule is optically inactive on account of internal compensation. It is not racemic (that is, it is not a mixture of two active forms), but it is inactive on account of the equal and opposite effects produced by the two similarly asymmetric ends of the same molecule.

Two dissimilar asymmetric carbon atoms in the same molecule give rise to four active stereoisomers and two racemic mixtures but no internally compensated form.

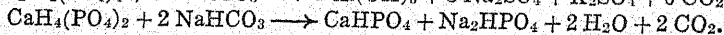
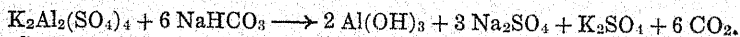
*Dextrotartaric acid* (m.p.  $170^\circ$ ) is obtained from grapes. It occurs in grape juice in the form of a potassium salt,  $\text{KHC}_4\text{H}_4\text{O}_6$  (cream of tartar), and precipitates when the juice ferments, on account of its insolubility in alcohol. This salt is used in the manufacture of baking powders:



The leavening of bread is accomplished by releasing carbon dioxide in the dough. In some baking powders pure tartaric acid is used with sodium bicarbonate:



In other powders alums or phosphates are substituted for the more expensive tartrate. The reactions of alum and phosphate powders are represented by the following equations:

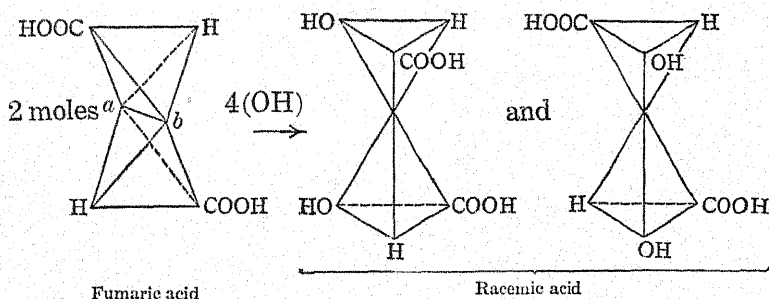


The sodium potassium salt  $\text{NaKC}_4\text{H}_4\text{O}_6$ , known as Rochelle salt, is used in making Fehling's solution and in Seidlitz powder.

When *d*-tartaric acid is boiled with an excess of sodium hydroxide, it is racemized, that is, converted into an equimolecular mixture of the dextro and lævo forms. The *racemic acid* thus formed, *dl*-tartaric, is optically inactive, but may be resolved into the active components by the methods devised by Pasteur (p. 117). *Lævotartaric acid* (m.p.  $170^\circ$ ) is obtained by these methods from racemic acid. *Mesotartaric acid*, inactive on account of internal compensation, cannot be resolved into active components. It is formed along with racemic acid, when *d*-tartaric acid is boiled with a solution of sodium hydroxide.

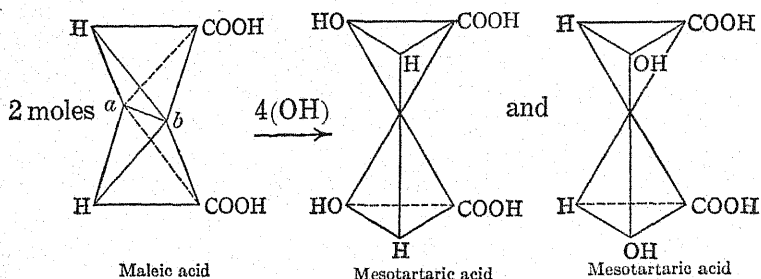
Relationships existing between fumaric, maleic, succinic, and tartaric acids are easily interpreted on the basis of the structural formulas given above.

When maleic acid is oxidized by potassium permanganate, mesotartaric acid is formed. Fumaric acid under the same treatment yields a mixture of dextrotartaric and lævotartaric acids (racemic acid). This is in strict harmony with the structure theory. The changes may be represented graphically as follows, but a clearer insight would be obtained by means of models:

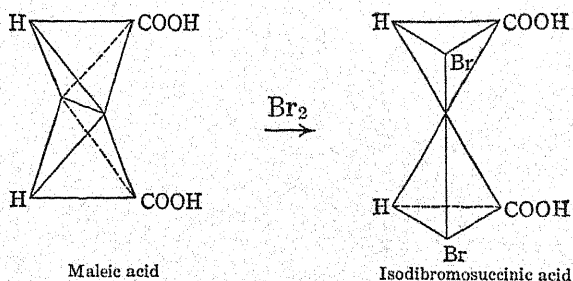


The structure formed by breaking the double bond at position *a* and introducing at that point a hydroxyl group on each carbon atom is the mirror image of the product formed by breaking the bond at *b*. Since the chances for breaking at these two points are exactly equal, the two forms are produced in equal quantities.

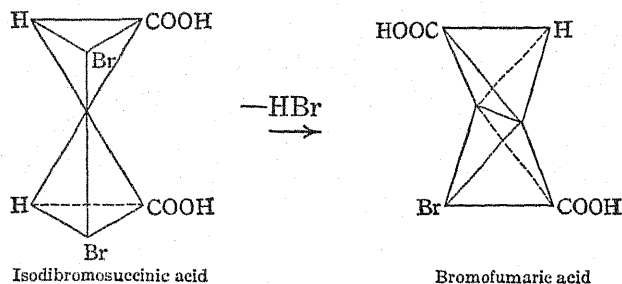
When maleic acid is oxidized by the addition of two hydroxyl groups, the same structure is formed, no matter which position is attacked, and this structure corresponds to the one assigned to mesotartaric acid on the basis of its failure to yield to the method employed for resolving inactive compounds into optically active components.



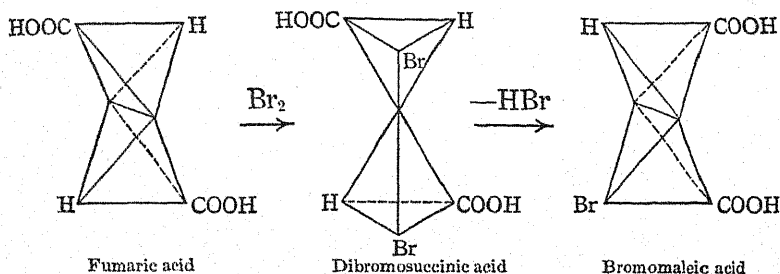
The principle of stereoisomerism accounts also for the results obtained when fumaric and maleic acids are treated with bromine. A dibromosuccinic acid is formed in each case, but the two products are not identical. The dibromosuccinic acid made from maleic acid, when warmed with alcoholic potash, loses a molecule of hydrobromic acid and is thereby converted into bromofumaric acid. On the other hand, fumaric acid gives rise to a dibromosuccinic acid, which loses hydrobromic acid with the formation of bromomaleic acid.



Rotation around the common axis of the two tetrahedra, to bring the hydrogen on one carbon atom over bromine on the other, must occur before HBr can be eliminated from this addition product. When this is done, the double bond is established with the carboxyl groups on opposite sides of the molecule.

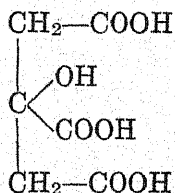


Beginning with fumaric acid, similar changes occur.



The dibromosuccinic acid which is derived from fumaric acid by treatment with bromine yields mesotartaric acid when the bromine atoms are replaced by hydroxyl groups through the action of a base. This is an unexpected result, for when fumaric acid acquires hydroxyl groups directly through the agency of an alkaline permanganate solution, racemic tartaric acid is formed. No satisfactory explanation of this anomaly has been made.

*Citric acid.* A crystalline tribasic acid,  $\text{C}_6\text{H}_8\text{O}_7$ , known as citric acid is obtained from the juice of lemons. The structure of the molecule is represented by the following formula:



The presence of an alcoholic hydroxyl group is indicated by the fact that the triethyl ester of citric acid reacts with acetyl chloride, forming an acetyl derivative of the ester.

## ALIPHATIC AMINES

The aliphatic amines are derivatives of ammonia in which hydrogen has been replaced by alkyl radicals. They are classified as primary, secondary, or tertiary, according to the number of hydrogen atoms replaced. General formulas for the three classes of amines may be written as follows:



Primary amine

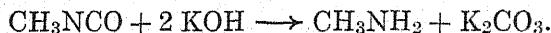


Secondary amine



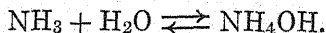
Tertiary amine

The simplest member of the class, methylamine,  $\text{CH}_3\text{NH}_2$ , was the first one discovered. It was isolated by Wurtz in 1848 from the hydrolysis products of methylisocyanate. The isocyanate was boiled with potassium hydroxide solution, and the amine was released as a gas:

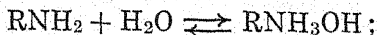


It has an odor similar to that of ammonia, is very soluble in water (1150 : 1 at  $12^\circ$ ), and, like ammonia, its solution in water is basic.

An equilibrium exists between ammonia and ammonium hydroxide in aqueous solution:



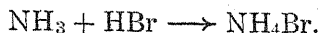
The ammonium hydroxide ionizes, yielding hydroxide ions, and by virtue of this ionization it precipitates iron and aluminum as hydroxides from solutions containing ions of these metals. The amines behave in the same way. They turn litmus blue and precipitate the hydroxides of iron and aluminum from aqueous solutions, owing to the establishment of the following equilibria:



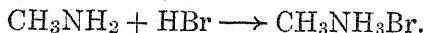
Methylamine is so much like ammonia in all its chemical and physical properties that it was mistaken for ammonia

when first produced and was identified as a different substance only after the observation was made that it burns in air.

To continue the analogy we may consider the addition reactions of ammonia and of amines. Ammonia combines with an acid to form an ammonium salt:

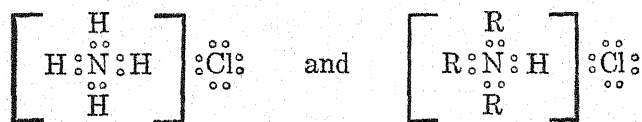


The amines react with acids in the same way to form substituted ammonium salts:



The structures of ammonium salts and of amine salts are identical. In each case four positive radicals are attached directly to the nitrogen atom and a negative ion is held by the ammonium ion through an entirely different type of bond.

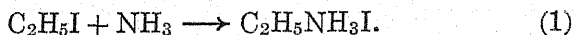
Nitrogen, belonging to the fifth group in the periodic system, has five electrons in its outer shell. The kernel of the atom has an equal positive charge. The valence of nitrogen is satisfied when an octet of electrons is formed around it, and this is accomplished when four atoms are bound to nitrogen by four pairs of electrons. The fifth element or group has no direct attachment to the nitrogen. It acquires from the nitrogen one electron and is held in the neighborhood of the positive ammonium radical without definite orientation. The formulas of ammonium chloride and of the hydrochloride of a tertiary amine may be written as follows:



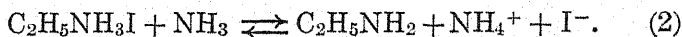
To emphasize the view that in ammonium compounds the negative atom or group is not attached directly to the nitrogen atom, formulas of the type  $\text{R}_4\text{N}(\text{X})$  or  $\text{R}_4\text{N}^+\text{X}^-$  will sometimes be used. The symbol R is used here to represent either an aliphatic or an aromatic carbon radical or a hydrogen atom. The small circles represent electrons.

**Preparation.** 1. The amines may be prepared by heating, in sealed tubes, alkyl halides and ammonia dissolved in alcohol (Hofmann's method). Secondary, as well as primary, alkyl halides may be used in this reaction. Mixtures of tertiary

alkyl halides and ammonia yield unsaturated hydrocarbons and ammonium salts. Primary and secondary alkyl halides yield olefines when warmed with alcoholic potash but do not ordinarily decompose in this manner in the presence of an excess of ammonia. The reaction between ammonia and an alkyl halide does not stop when one hydrogen atom of the ammonia molecule has been replaced. Another alkyl halide molecule reacts with the primary amine,  $\text{RNH}_2$ , replacing one more hydrogen atom, with the formation of a secondary amine,  $\text{R}_2\text{NH}$ . This in turn yields a tertiary amine,  $\text{R}_3\text{N}$ , in which the three hydrogen atoms of ammonia have all been replaced by alkyl groups. The reactions occur as follows:



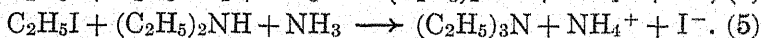
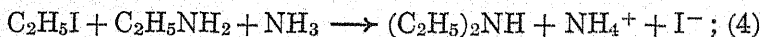
The ethyl ammonium iodide,  $\text{C}_2\text{H}_5\text{NH}_3\text{I}$ , in the presence of ammonia is in equilibrium with ethylamine and the ions of ammonium iodide:



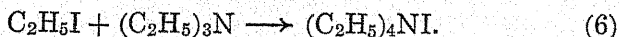
We may therefore combine reactions (1) and (2):



This is followed by reactions in which amines combine with the alkyl halide:

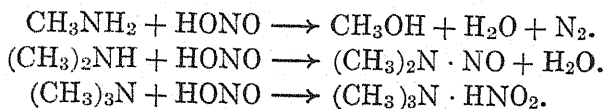


Finally, through the addition of the alkyl halide to the tertiary amine, a quaternary ammonium salt is formed:



The Hofmann method leads to the formation of a mixture of primary, secondary, and tertiary amines, together with quaternary ammonium salts. Various methods have been devised for isolating pure amines from the mixture. Most of these methods involve the decomposition and loss of at least one of the products. The first step in the separation is generally accomplished by distilling the alkaline solution with steam. The quaternary ammonium salt,  $\text{R}_4\text{NX}$ , is nonvolatile and remains in the distilling flask. The free primary, secondary, and tertiary amines pass over with steam. Nitrous acid acts upon the distillate, converting the primary amine into an alcohol, forming

a nitroso compound with the secondary amine and a salt with the tertiary compound:

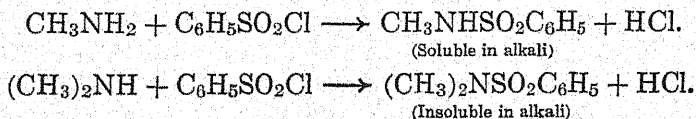


The nitroso derivative of the secondary amine usually separates as an oily layer, which can be removed with the aid of a separatory funnel. If it fails to appear as a distinct layer, it is removed from the acid solution by extraction with ether. The free amine is obtained from the nitrosoamine by boiling the latter with an aqueous solution of a strong acid, the original reaction being reversed by the elimination of nitrous acid at the higher temperature:



The primary amine is lost, having been converted into an alcohol, from which it is not easily regenerated. The tertiary amine is liberated from the salt by treatment with a base and it is obtained in the free state by extraction with ether or by distillation.

The most satisfactory general method for separating primary, secondary, and tertiary amines without loss of one of them depends upon their reactions with benzenesulfonyl chloride,  $\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$ . This reagent is a colorless liquid which fumes when exposed to moist air. Its preparation will be described later. The mixed amines, separated from the quaternary salt as indicated above, are treated with benzenesulfonyl chloride and potassium hydroxide solution. Primary amines yield products which are soluble in the alkali, secondary amines yield insoluble products, and the tertiary compounds are unchanged:\*

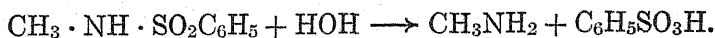


The insoluble derivative of the secondary amine is removed from the mixture by mechanical means. The unchanged tertiary amine and the sulfonamide derived from the primary amine

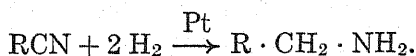
\* Trimethylamine is an exception. It forms a salt with benzenesulfonyl chloride. Vorlander and Nolte, *Ber.*, **46**, 3212 (1913).



are separated by distillation, the free tertiary amine being much more volatile than the sodium salt of the compound derived from the primary amine. The free primary and secondary amines are obtained from these derivatives by hydrolysis. The hydrolysis is accomplished by boiling the compound with an acid : \*

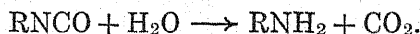


2. Primary amines may be prepared free from secondary and tertiary compounds by reduction of nitriles (alkyl cyanides) with hydrogen in the presence of finely divided platinum at  $200^\circ$  or by the action of sodium on an alcoholic solution of the nitrile :

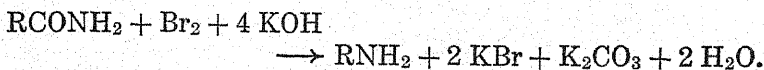


3. Amines are formed through the reduction of nitroparaffins by sodium amalgam in alcohol or by zinc or tin in hydrochloric acid. This reaction is of little importance in the preparation of aliphatic amines, but constitutes the best method for making the corresponding aromatic compounds. This procedure will be illustrated later.

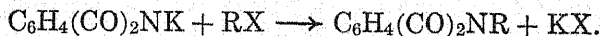
4. Amines are formed when isocyanates are hydrolyzed by boiling them with dilute alkali :



5. The action of bromine and an alkali on an acid amide results in the formation of an amine. The net result of the reaction is indicated by the equation given below, but consideration of the mechanism by which it is accomplished is reserved for later treatment :

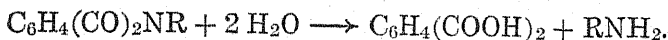


6. A general method for preparing a pure primary amine is based upon Gabriel's phthalimide reaction. Potassium phthalimide,  $\text{C}_6\text{H}_4(\text{CO})_2\text{NK}$ , combines with alkyl halides as follows :



\* Hinsberg, *Ber.*, 38, 906 (1905). In the acid solution the amine is converted into a salt, but it can be obtained in the free state by warming the salt with a base, just as ammonia can be obtained from an ammonium salt by treatment with a base.

The product when hydrolyzed yields phthalic acid and a primary amine:

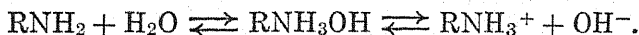


The details of this process are outlined on page 418.

**Properties.** The amines of low molecular weight are gases, the intermediate members are liquids, and those of high molecular weight are solids. Volatility and solubility decrease as the molecular weights increase.

The hydrates of the primary, secondary, and tertiary amines act like weak bases, for, like ammonium hydroxide, they lose water and exist largely in the form of free amines in aqueous solution. The quaternary bases cannot lose water in the same way, for in these compounds there is no hydrogen attached to the nitrogen atom. They are strong bases, being almost completely ionized in dilute solutions.

The following equilibria are established with amines in water:



We do not know how much of the amine is in the form of  $\text{RNH}_3\text{OH}$ . We have no means of distinguishing between  $\text{RNH}_2$  dissolved as such in water and the hydrated form. We are therefore unable to evaluate the first of the two equilibria. We are able to determine the concentration of the hydroxide ions in solution by means of indicators, and we can determine the sum of all forms of the amine in solution by titration. The dissociation constants of amines as bases are calculated from the equation

$$K_b = \frac{(\text{RNH}_3^+)(\text{OH}^-)}{(\text{RNH}_2) + (\text{RNH}_3\text{OH})}.$$

In applying this formula the concentrations of the ions and molecules represented by formulas in parentheses are expressed in moles per liter. The denominator,  $(\text{RNH}_2) + (\text{RNH}_3\text{OH})$ , represents the total number of moles per liter of the base in solution minus the number of moles that have dissociated. If  $B$  represents the total base in solution in all forms, the equation may be written

$$K_b = \frac{(\text{RNH}_3^+)(\text{OH}^-)}{B - (\text{OH}^-)} = \frac{(\text{OH}^-)^2}{B - (\text{OH}^-)}.$$

In weak bases  $B - (OH^-)$  has nearly the same value as  $B$ , and the equation is often used in the form

$$K_b = \frac{(OH^-)^2}{B}$$

The constants for a few amines are given in the following table:

| NAME                     | FORMULA        | $K_b$                | MOLES OF $OH^-$ PER LITER IN A 0.1 M SOLUTION |
|--------------------------|----------------|----------------------|---|
| Ammonia . . . . .        | $NH_3$         | $1.9 \times 10^{-5}$ | $1.4 \times 10^{-3}$                          |
| Methylamine . . . . .    | $CH_3NH_2$     | $5 \times 10^{-4}$   | $6.9 \times 10^{-3}$                          |
| Dimethylamine . . . . .  | $(CH_3)_2NH$   | $7.4 \times 10^{-4}$ | $8.6 \times 10^{-3}$                          |
| Trimethylamine . . . . . | $(CH_3)_3N$    | $7.4 \times 10^{-5}$ | $2.7 \times 10^{-3}$                          |
| Ethylamine . . . . .     | $C_2H_5NH_2$   | $5.6 \times 10^{-4}$ | $7.2 \times 10^{-3}$                          |
| Diethylamine . . . . .   | $(C_2H_5)_2NH$ | $1.3 \times 10^{-3}$ | $1.1 \times 10^{-2}$                          |
| Triethylamine . . . . .  | $(C_2H_5)_3N$  | $6.4 \times 10^{-4}$ | $8 \times 10^{-3}$                            |

To calculate the concentration of hydroxide ions in a 0.2 M solution of trimethylamine, the constant  $K_b$  is used as follows:

$$\frac{(OH^-)^2}{0.2} = 7.4 \times 10^{-5},$$

$$(OH^-)^2 = 1.48 \times 10^{-5},$$

$$(OH^-) = \sqrt{1.48 \times 10^{-5}} = 3.84 \times 10^{-3} \text{ moles per liter.}$$

$$\text{Fraction of the base ionized} = \frac{3.84 \times 10^{-3}}{0.2}.$$

$$\text{Per cent ionized} = \frac{3.84 \times 10^{-3}}{0.2} \times 100 = 1.92\%.$$

In this estimation the concentration of  $OH^-$  ions was considered negligible as compared with the total quantity of base present. A more accurate calculation is made as follows:

$$\frac{(OH^-)^2}{0.2 - (OH^-)} = 7.4 \times 10^{-5},$$

$$(OH^-)^2 = (1.48 \times 10^{-5}) - (7.4 \times 10^{-5})(OH^-),$$

$$(OH^-)^2 + (7.4 \times 10^{-5})(OH^-) - (1.48 \times 10^{-5}) = 0.$$

This is a quadratic equation corresponding to the form

$$ax^2 + bx + c = 0;$$

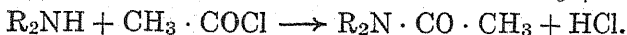
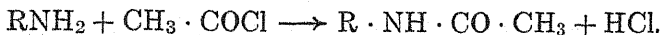
$$\text{the solution is } x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}.$$

$$\begin{aligned} \text{Then } (OH^-) &= \frac{-(7.4 \times 10^{-5}) \pm \sqrt{(54.8 \times 10^{-10}) + (5.92 \times 10^{-5})}}{2} \\ &= \frac{-(7.4 \times 10^{-5}) \pm \sqrt{(0.00548 \times 10^{-6}) + (59.2 \times 10^{-6})}}{2} \\ &= \frac{-(0.074 \times 10^{-3}) \pm (7.69 \times 10^{-3})}{2} \\ &= 3.81 \times 10^{-3} \text{ moles per liter.} \end{aligned}$$

$$\text{Fraction ionized} = \frac{3.81 \times 10^{-3}}{0.2}.$$

$$\text{Per cent ionized} = \frac{3.81 \times 10^{-3}}{0.2} \times 100 = \frac{3.81 \times 10^{-1}}{0.2} = 1.90\%.$$

The primary and secondary amines react with acid chlorides as do the alcohols:

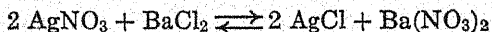


In some cases both hydrogen atoms in the primary amino group are replaced by acyl radicals; but usually only one is removed, as indicated in the equation. The products (substituted amides) are easily crystallized and purified, and are therefore readily identified.

The boiling points of a few amines are given below:

| NAME                     | MONO-   | DI-    | TRI-   |
|--------------------------|---------|--------|--------|
| Methylamine . . . . .    | - 6.5°  | + 7.4° | + 3.5° |
| Ethylamine . . . . .     | + 16.6° | 56°    | 89.5°  |
| Normal propylamine . .   | 48.7°   | 110.7° | 156°   |
| Isopropylamine . . . .   | 34°     | 84°    | —      |
| Normal butylamine . . .  | 76°     | 161°   | 214°   |
| Isobutylamine . . . . .  | 68°     | 138.8° | 191.5° |
| Secondary butylamine . . | 63°     | 132°   | —      |
| Tertiary butylamine . .  | 43.8°   | —      | —      |
| Normal amylamine . . .   | 104°    | —      | —      |
| Isoamylamine . . . . .   | 95°     | 190°   | 237°   |

The ammonia system. Franklin has called attention to remarkable analogies between the properties of water and ammonia and has developed what is known as the ammonia system. Water and liquid ammonia are good ionizing solvents. Ionic reactions may be carried out in liquid ammonia as well as in water. For instance, silver chloride is precipitated from an aqueous solution of silver nitrate by the addition of barium chloride, because of the insolubility of silver chloride in water. In liquid ammonia silver chloride, silver nitrate, and barium nitrate are soluble, and barium chloride is insoluble. The equation



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The constants for a few amines are given in the following table:

| NAME                     | FORMULA        | $K_b$                | MOLES OF $OH^-$ PER LITER IN A 0.1 M SOLUTION |
|--------------------------|----------------|----------------------|---|
| Ammonia . . . . .        | $NH_3$         | $1.9 \times 10^{-5}$ | $1.4 \times 10^{-3}$                          |
| Methylamine . . . . .    | $CH_3NH_2$     | $5 \times 10^{-4}$   | $6.9 \times 10^{-3}$                          |
| Dimethylamine . . . . .  | $(CH_3)_2NH$   | $7.4 \times 10^{-4}$ | $8.6 \times 10^{-3}$                          |
| Trimethylamine . . . . . | $(CH_3)_3N$    | $7.4 \times 10^{-5}$ | $2.7 \times 10^{-3}$                          |
| Ethylamine . . . . .     | $C_2H_5NH_2$   | $5.6 \times 10^{-4}$ | $7.2 \times 10^{-3}$                          |
| Diethylamine . . . . .   | $(C_2H_5)_2NH$ | $1.3 \times 10^{-3}$ | $1.1 \times 10^{-2}$                          |
| Triethylamine . . . . .  | $(C_2H_5)_3N$  | $6.4 \times 10^{-4}$ | $8 \times 10^{-3}$                            |

To calculate the concentration of hydroxide ions in a 0.2 M solution of trimethylamine, the constant  $K_b$  is used as follows:

$$\frac{(OH^-)^2}{0.2} = 7.4 \times 10^{-5},$$

$$(OH^-)^2 = 1.48 \times 10^{-5},$$

$$(OH^-) = \sqrt{1.48 \times 10^{-5}} = 3.84 \times 10^{-3} \text{ moles per liter.}$$

$$\text{Fraction of the base ionized} = \frac{3.84 \times 10^{-3}}{0.2}.$$

$$\text{Per cent ionized} = \frac{3.84 \times 10^{-3}}{0.2} \times 100 = 1.92 \%.$$

In this estimation the concentration of  $OH^-$  ions was considered negligible as compared with the total quantity of base present. A more accurate calculation is made as follows:

$$\frac{(OH^-)^2}{0.2 - (OH^-)} = 7.4 \times 10^{-5},$$

$$(OH^-)^2 = (1.48 \times 10^{-5}) - (7.4 \times 10^{-5})(OH^-),$$

$$(OH^-)^2 + (7.4 \times 10^{-5})(OH^-) - (1.48 \times 10^{-5}) = 0.$$

This is a quadratic equation corresponding to the form

$$ax^2 + bx + c = 0;$$

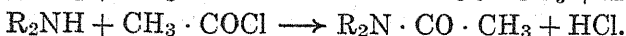
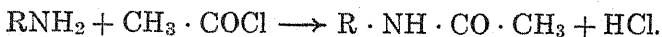
$$\text{the solution is } x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}.$$

$$\begin{aligned} \text{Then } (OH^-) &= \frac{-(7.4 \times 10^{-5}) \pm \sqrt{(54.8 \times 10^{-10}) + (5.92 \times 10^{-5})}}{2} \\ &= \frac{-(7.4 \times 10^{-5}) \pm \sqrt{(0.00548 \times 10^{-6}) + (59.2 \times 10^{-6})}}{2} \\ &= \frac{-(0.074 \times 10^{-3}) \pm (7.69 \times 10^{-3})}{2} \\ &= 3.81 \times 10^{-3} \text{ moles per liter.} \end{aligned}$$

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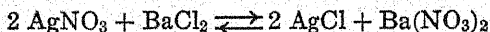


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The boiling points of a few amines are given below:

| NAME                     | MONO-   | DI-    | TRI-   |
|--------------------------|---------|--------|--------|
| Methylamine . . . . .    | - 6.5°  | + 7.4° | + 3.5° |
| Ethylamine . . . . .     | + 16.6° | 56°    | 89.5°  |
| Normal propylamine . .   | 48.7°   | 110.7° | 156°   |
| Isopropylamine . . . .   | 34°     | 84°    | —      |
| Normal butylamine . . .  | 76°     | 161°   | 214°   |
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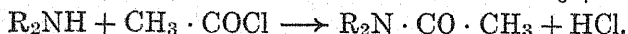
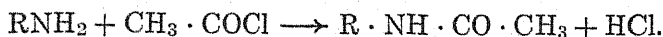
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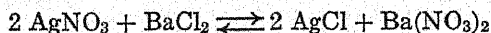


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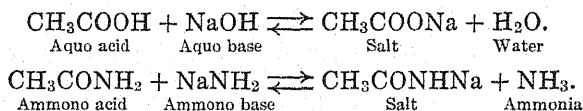
The ordinary oxygen acids are considered as derivatives of water in which hydrogen has been replaced by a nonmetallic element or



by a negative radical. Acetic acid, for example, is water in which a hydrogen atom has been replaced by the acetyl group,  $\text{CH}_3\text{CO}-$ . If the same group is substituted for hydrogen in ammonia, we obtain the amide,  $\text{CH}_3\text{CONH}_2$ , or the imide,  $(\text{CH}_3\text{CO})_2\text{NH}$ , and these are acids in the ammonia system. That is to say, they bear the same relationship to ammonia that ordinary acids bear to water.

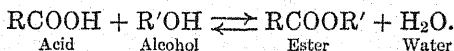
Bases, such as  $\text{NaOH}$  and  $\text{Ba}(\text{OH})_2$ , are derivatives of water in which hydrogen atoms have been replaced by metals. Similarly, compounds like sodium amide,  $\text{NaNH}_2$ , and barium imide,  $\text{BaNH}$ , represent derivatives of ammonia in which hydrogen atoms have been replaced by metals. They are bases in the ammonia system.

Ordinary acids and bases react to form salts and water; and, in the same way, ammono acids and bases yield ammono salts and ammonia:

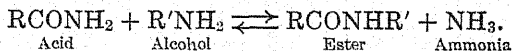


Acid amides and imides are the acids of the ammonia system. Metallic amides, imides, and nitrides are the bases; and metallic derivatives of the acid amides and imides are the corresponding salts.

An ester is formed, in the water system, through the action of an acid on an alcohol, and by hydrolysis the ester may be reconverted into the original acid and alcohol, the reaction being reversible:



In the ammonia system the corresponding reagents and products are amides, amines, substituted amides (ammono esters), and ammonia; and the process of reconvertng the ammono ester into the ammono acid and amine is called ammonolysis:

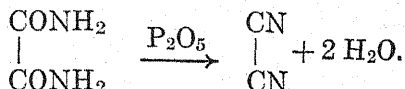


For a complete treatment of this subject see E. C. Franklin's "The Ammonia System of Compounds." Reinhold Pub. Corp., 1935.

## CYANIDES AND CYANATES

The principal derivatives of cyanogen are the cyanides or nitriles,  $\text{RCN}$ ; the isocyanides or carbylamines,  $\text{RNC}$ ; the cyanates,  $\text{ROCN}$ ; the isocyanates,  $\text{RNCO}$ ; and the fulminates,  $\text{RONC}$ .

*Cyanogen*,  $\text{C}_2\text{N}_2$  (m.p.  $-34.4^\circ$ , b.p.  $-20.7^\circ$ ), is a colorless, poisonous gas, fairly soluble in water (4 : 1 by volume) and very soluble in alcohol (23 : 1). It burns with a purple flame. Its formation from oxamide by dehydration indicates its structure:



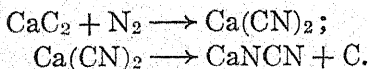
It is usually made by heating a solution of potassium cyanide with copper sulfate. The cupric cyanide first formed decomposes, yielding cuprous cyanide and cyanogen.

## CYANIDES AND ISOCYANIDES

*Hydrogen cyanide*, or prussic acid,  $\text{HCN}$  (m.p.  $-14^\circ$ , b.p.  $26^\circ$ ), is a colorless, poisonous liquid, having an odor resembling that of almond oil. It has a high dielectric constant and is a good ionizing solvent for many inorganic salts. Prussic acid occurs as a glucoside in bitter almonds and in the seeds of many tropical plants.

Hydrocyanic acid is ten thousand times weaker than acetic acid. The dissociation constants are  $1.3 \times 10^{-9}$  and  $1.8 \times 10^{-5}$  respectively. The salts of hydrocyanic acid are decomposed by carbonic acid.

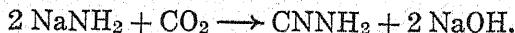
Many processes have been devised for using atmospheric nitrogen as a source of cyanides. Calcium carbide, when heated in an atmosphere of nitrogen, is converted into calcium cyanide and calcium cyanamide:



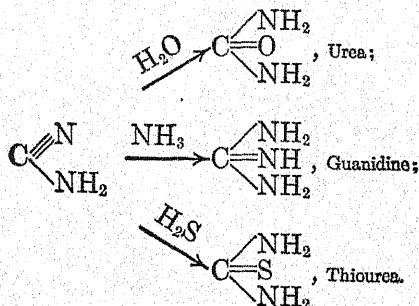
*Calcium cyanamide* is manufactured in enormous quantities for use as a fertilizer. When applied to the soil it undergoes hydrolysis to cyanamide, which in turn is converted into urea and ammonium salts. Under the influence of nitrifying bacteria present in all productive soils, ammonium salts are converted into nitrites and ultimately into nitrates, and thus nitrogen withdrawn from the air through the agency of calcium carbide becomes available to plants. Calcium carbide prepared from lime and coke in an electric furnace is pulverized, then reheated in an atmosphere of nitrogen. Enough heat is evolved in the reaction to maintain the nitrifying ovens at the proper temperature.

The nitrogen used is obtained from the atmosphere (1) by distillation of liquid air (the first fraction is largely nitrogen) or (2) by passing air over red-hot, finely divided copper on asbestos. The copper oxide is reduced by hot natural gas without removing it from the tubes, so that the same copper can be used repeatedly.

*Cyanamide*,  $\text{C} \begin{array}{l} \text{N} \\ \text{NH}_2 \end{array}$ , is a colorless crystalline substance (m.p.  $44^\circ$ ). The usual laboratory method for making it in small quantities consists in passing carbon dioxide over hot sodium amide:

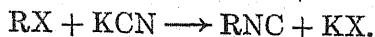
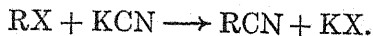


Cyanamide combines with water to form urea. With ammonia it yields guanidine, and with hydrogen sulfide it forms thiourea:



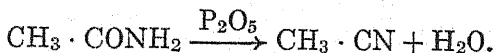
In an ammoniacal solution of a silver salt it forms a yellow precipitate,  $\text{CN} \cdot \text{NAg}_2$ .

Potassium cyanide reacts with alkyl halides in alcoholic solution, yielding alkyl cyanides or nitriles,  $\text{RCN}$ , mixed with smaller amounts of isocyanides or carbylamines,  $\text{RNC}$  : \*

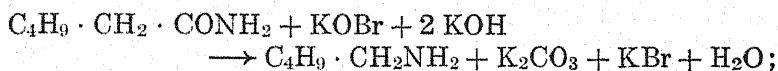


The isocyanides are converted into the normal compounds when heated to  $250^\circ$ .

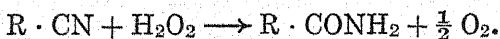
Nitriles may be obtained from amides by heating the latter with phosphorus pentoxide :



Many amides may be converted into nitriles by bromine and potassium hydroxide. An amine is first formed,† and with the lower members the amine is the final product :



The alkyl cyanides are readily hydrolyzed to amides or to acids. Boiling with acids or alkalies usually carries the hydrolysis to completion ; that is to say, acids or salts of acids are produced. Warming cyanides with hydrogen peroxide often results in the formation of amides :



Reduction by sodium amalgam in alcoholic solution or by hydrogen in contact with hot nickel converts a cyanide into an amine :



These reactions all indicate that the carbon of the cyanide radical is linked directly to carbon in the alkyl group. In other words, the formula of a nitrile is  $\text{RCN}$  and not  $\text{RNC}$ .

The nitriles are derived indirectly from alcohols or directly from alkyl halides and they are readily hydrolyzed to acids or reduced to amines. They are named with reference either

\* Hydrocyanic acid is itself a tautomeric substance,  $\text{H} \cdot \text{C} : \text{N}$  and  $\text{H} \cdot \text{N} : \text{C}$ , and nearly all its derivatives are capable of existence in two forms.

† See Hofmann Rearrangement, p. 431.

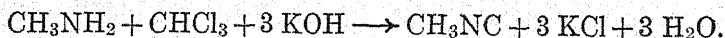
to the alkyl halides from which they are derived or to the acids which they form. Thus  $\text{CH}_3\text{CN}$  is either methyl cyanide or acetonitrile; and  $\text{C}_2\text{H}_5\text{CN}$  is ethyl cyanide or propionitrile.

## CYANIDES OR NITRILES

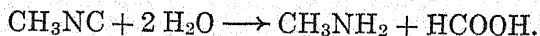
| NAME                                   | FORMULA   | BOILING POINT |
|--|---|---------------|
| Acetonitrile . . . . .                 | $\text{CH}_3\text{CN}$  | $82^\circ$    |
| Propionitrile . . . . .                | $\text{CH}_3 \cdot \text{CH}_2\text{CN}$  | $97.1^\circ$  |
| Butyronitrile ( <i>n</i> ) . . . . .   | $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CN}$                         | $118^\circ$   |
| Butyronitrile ( <i>iso</i> ) . . . . . | $(\text{CH}_3)_2\text{CHCN}$  | $108^\circ$   |
| Valeronitrile ( <i>n</i> ) . . . . .   | $\text{CH}_3(\text{CH}_2)_3\text{CN}$   | $141^\circ$   |
| Isopropylacetonitrile . . . . .        | $(\text{CH}_3)_2\text{CH} \cdot \text{CH}_2\text{CN}$                                     | $129.3^\circ$ |
| Methylethylacetonitrile . . . . .      | $\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{C}_2\text{H}_5 \end{array} \text{CHCN}$ | $125^\circ$   |
| Trimethylacetonitrile . . . . .        | $(\text{CH}_3)_3\text{CCN}$   | $106^\circ$   |
| Isobutylacetonitrile . . . . .         | $(\text{CH}_3)_2\text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2\text{CN}$                   | $155.5^\circ$ |
| Diethylacetonitrile . . . . .          | $(\text{C}_2\text{H}_5)_2\text{CHCN}$   | $146^\circ$   |

*Methyl cyanide*,  $\text{CH}_3 \cdot \text{CN}$  (m.p.  $-41^\circ$ ), a liquid having a pleasant odor, is prepared by distilling acetamide with phosphorus pentoxide. *Ethyl cyanide*,  $\text{C}_2\text{H}_5 \cdot \text{CN}$  (m.p.  $-103^\circ$ ), is made in the same way from the amide of propionic acid. All members of the series containing fewer than five carbon atoms and most of the higher members are liquids somewhat lighter than water and only sparingly soluble in water. Trimethylacetonitrile is a solid (m.p.  $16^\circ$ ). Myristonitrile,  $\text{C}_{13}\text{H}_{27}\text{CN}$ , melts at  $19^\circ$ ; palmitonitrile,  $\text{C}_{15}\text{H}_{31}\text{CN}$ , at  $29^\circ$ ; stearonitrile,  $\text{C}_{17}\text{H}_{35}\text{CN}$ , at  $41^\circ$ ; and margaritrile or cetyl cyanide,  $\text{C}_{16}\text{H}_{33}\text{CN}$ , at  $53^\circ$ .

The isocyanides or carbylamines are liquids characterized by persistent and offensive odors. They are produced from primary amines by the action of chloroform and an alkali in alcoholic solution:

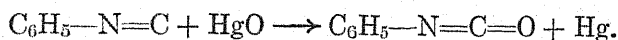


Cold dilute acids hydrolyze carbylamines to amines and formic acid:



They are not hydrolyzed by alkalis even when warmed. The normal cyanides, on the other hand, are hydrolyzed by either acids or alkalis.

The formula  $R-N=C$  for an isocyanide was established by Nef.\* It was formerly written  $R-N\equiv C$ , but there is no evidence for the existence of a quadruple bond between atoms in any compound; and there is an abundance of evidence for the existence of compounds of bivalent carbon. That the carbon atom is unsaturated in an isocyanide is indicated by the fact that phenylisocyanide,  $C_6H_5-N=C$ , forms an addition product with chlorine, having the structure  $C_6H_5-N=CCl_2$ ; and is oxidized to an isocyanate by mercuric oxide:

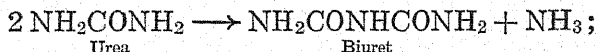


In these reactions additions occur on the carbon atom exclusively, and there are many other examples of the same type. If a multiple bond were broken, the added atoms would be shared by two elements instead of going to one alone.

### CYANATES, ISOCYANATES, AND FULMINATES

*Cyanic acid*,  $HO-CN$ , derived from cyanuric acid,  $(HO-CN)_3$ , as explained in the next paragraph, is an extremely unstable liquid. At temperatures above zero it polymerizes to an amorphous solid composed of cyamelide,  $(HNCO)_3$ , and cyanuric acid,  $(HNCO)_3$ . A solution of the acid in water is also unstable, changing spontaneously at ordinary temperatures into carbon dioxide and ammonia.

*Cyanuric acid* is made by heating urea. Biuret is first formed, but this reacts with another molecule of urea, forming cyanuric acid:

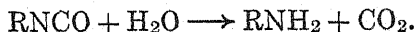


Cyanic acid is obtained by distilling cyanuric acid and cooling the distillate to a temperature below zero.

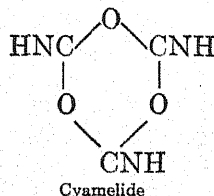
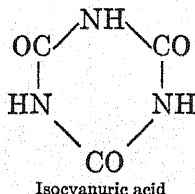
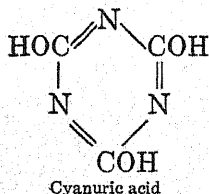
The constitution of cyanic acid has not been definitely established. It is either  $H-O-C\equiv N$  or  $H-N=C=O$  or an equilibrium mixture of the two. It forms two series of derivatives, those corresponding to the formula  $HO-CN$ , called normal cyanates, and derivatives of  $HNCO$ , known as isocyanates.

\* Nef, *Ann.*, 270, 267 (1892); *ibid.*, 287, 265 (1895).

Esters of normal cyanic acid have not been isolated, for they polymerize as rapidly as formed, producing esters of cyanuric acid. Esters of isocyanic acid are well known. They are liquids having disagreeable odors. They polymerize to isocyanuric esters when heated and are hydrolyzed by water to carbon dioxide and amines:



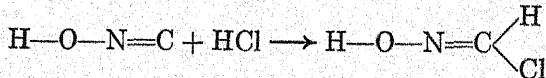
*Cyamelide*, mentioned above as one of the polymerization products of cyanic acid, is a stable, nonvolatile, and insoluble solid substance. It is formed rapidly and spontaneously from the vapor of cyanic acid at ordinary temperatures. At higher temperatures cyanuric acid is formed. Cyamelide is converted into cyanuric acid by hot alkalis; but cyanuric acid can be changed back to cyamelide only through the formation of cyanic acid as an intermediate product. The formulas assigned to these substances are



but there is still doubt as to the validity of these structures.

*Fulminic acid*,  $\text{H}-\text{O}-\text{N}=\text{C}$ , has not been isolated in the free state. Its salts are more stable, but even the salts of fulminic acid must be handled with care. They are easily detonated, and in fact their only practical value depends upon this property. Mercury fulminate,  $\text{Hg}(\text{ONC})_2$ , is used in percussion caps for firearms and in the caps used in connection with fuses for firing blasting gelatin and dynamite.

Hydrochloric acid combines with fulminic acid, yielding the oxime of formyl chloride in the form of large, colorless crystals which rapidly vanish by evaporation, even at room temperature:



This reaction, coupled with the fact that fulminic acid and many of its derivatives yield hydroxylamine on hydrolysis, indicates the presence of the  $=\text{NOH}$  group in all fulminates.

## THE CARBOHYDRATES

From the standpoint of plant life the carbohydrates are the most important compounds in nature; for the major part of the solid matter in all plant tissues is made up of representatives of this group. Cellulose, starch, and sugar are typical carbohydrates.

The name implies that these compounds are hydrates of carbon; it was, in fact, chosen to convey that idea. Sugars are now known, however, in which hydrogen and oxygen are not present in the same ratio as in water. Examples are rhamnose and fucose, each having the formula  $C_6H_{12}O_5$ . On the other hand, there are many compounds consisting of carbon, hydrogen, and oxygen, with formulas of the type  $C_nH_{2n}O_n$ , that are not related to the sugars and would never be classed as carbohydrates on the basis of physical or chemical properties. Examples are formaldehyde,  $CH_2O$ ; acetic acid,  $C_2H_4O_2$ ; and lactic acid,  $C_3H_6O_3$ . The term *carbohydrate*, therefore, is not a well-chosen name for the class of compounds comprising the sugars and starches. The simple sugars are polyhydric alcohols and they are also aldehydes or ketones. The more complex sugars and the starches and celluloses are condensation products of the simple sugars. The union of simple sugar molecules to form higher sugars and starches is accomplished through carbonyl groups, and, as a consequence, the condensation products may or may not display the properties of aldehydes or of ketones. They all possess alcoholic hydroxyl groups, and they are all converted into simple sugars by hydrolysis. We shall continue to classify the sugars, starches, and celluloses as carbohydrates, but we shall think of them not as hydrates of carbon but as aldehyde alcohols or ketone alcohols or compounds that, upon hydrolysis, yield aldehyde alcohols or ketone alcohols.

The carbohydrates fall into two principal classes: (1) the crystalline, soluble, and sweet carbohydrates of comparatively low molecular weights known as sugars, and (2) the amorphous, tasteless, and more or less insoluble bodies called cel-



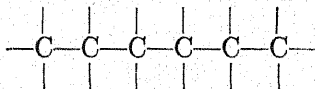
luloses and starches. They are classified also as monosaccharides, disaccharides, and polysaccharides. The monosaccharides include the simple sugars, such as glucose and fructose, and all carbohydrates that cannot be hydrolyzed with the production of smaller units. The disaccharides, such as cane sugar, milk sugar, and maltose, are made up of two smaller carbohydrate molecules, and each polysaccharide is composed of more than two monosaccharide molecules.

Although the only important monosaccharides are the sugars having five or six carbon atoms in the molecule, representatives of the class are known with from three to ten carbon atoms. The names *triose*, *tetrose*, *pentose*, and so on are used to designate these subclasses. The terms *aldose* and *ketose* are used to distinguish the aldehyde alcohols from the ketone alcohols. Thus, if a monosaccharide is a ketone alcohol of six carbon atoms, it is called a ketohexose; an aldehyde alcohol of five carbon atoms is an aldopentose.

In order to ascertain the structure of a simple sugar, let us consider the following facts which apply to all aldohexoses:

1. By analysis and molecular-weight determinations the compound is found to have the empirical formula  $C_6H_{12}O_6$ .

2. It is reduced by hydrogen iodide to normal hexane or to normal hexyl iodide. Therefore the six carbon atoms form a continuous chain,

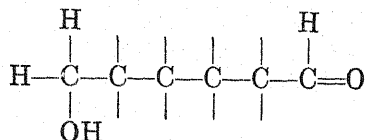


3. It forms an addition product with one and only one molecule of hydrogen cyanide. It forms an oxime with hydroxylamine and a hydrazone with phenylhydrazine. It therefore has one carbonyl group. It is either an aldehyde or a ketone.

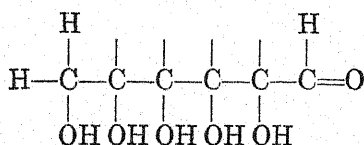
4. Gentle oxidation converts it into a monobasic acid having the same number of carbon atoms. At the same time the properties referred to in the last paragraph disappear. The sugar is, therefore, an aldehyde, and since the group CHO is univalent, the carbon atom in this group is terminal; that is, it is at the end of the chain.

5. The monobasic acid referred to in the last paragraph is oxidized by nitric acid to a dibasic acid ( $C_6H_{10}O_8$ ). The sugar has, therefore, a primary alcohol group, for, by oxidation, two carboxyl groups are formed without loss of carbon, and only

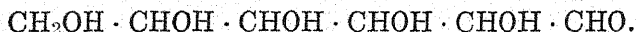
one aldehyde group is present in the unoxidized molecule. This  $\text{CH}_2\text{OH}$  group, being univalent, must be terminal. We have then



6. The sugar reacts with acetic anhydride or with acetyl chloride, forming a penta-acetyl derivative, indicating the presence of five hydroxyl groups. Stable compounds having two hydroxyl groups attached to the same carbon atom are exceedingly rare; and the few that exist behave like aldehydes. The hexahydric alcohol derived from an aldohexose, by reduction, has no aldehydic properties. Hence we must conclude that only one hydroxyl group is attached to each of five carbon atoms, and the formula as determined up to this point is



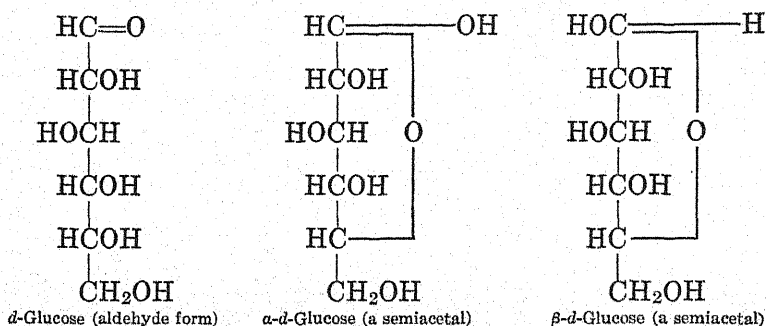
7. The empirical formula  $\text{C}_6\text{H}_{12}\text{O}_6$  indicates that four other hydrogen atoms are present in the molecule, and it is obvious that they must be held by the four central carbon atoms. The formula, therefore, for any aldohexose must be



There are four asymmetric carbon atoms in this formula, and therefore sixteen stereoisomeric compounds having this structure should exist. (See page 117.)

**Mutarotation.** Two dextrorotatory and two laevorotatory forms of glucose are known. They are called  $\alpha$ -*d*-glucose,  $\beta$ -*d*-glucose,  $\alpha$ -*l*-glucose, and  $\beta$ -*l*-glucose. The  $\alpha$  form of the dextrorotatory glucose ( $\alpha$ -*d*-glucose) is obtained by dissolving any sample of *d*-glucose in water and allowing it to crystallize through evaporation of the solvent. The  $\beta$  form is obtained by crystallizing *d*-glucose from pyridine or acetic acid. The laevorotatory forms of glucose are synthetic products — they are

not found among the naturally occurring sugars. A freshly prepared aqueous solution of  $\alpha$ -*d*-glucose has a specific rotation of  $113.4^\circ$ , and a freshly prepared aqueous solution of the  $\beta$ -*d*-glucose has a specific rotation of  $19.8^\circ$ . Both solutions gradually change in rotatory power until the intermediate value ( $52.7^\circ$ ) is reached. The phenomenon of change in this optical property is called *mutarotation*. It is displayed by all pentoses and hexoses. To account for it we assume that the monosaccharides exist mainly in the form of semiacetals having ring structures. Using the formula for *d*-glucose as an example, we have the following possible structures:

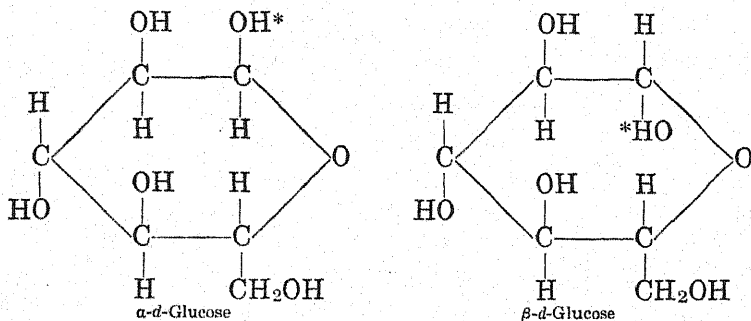


Acetals are produced in reactions between aldehydes and alcohols. In this case the two reacting groups, CHO and OH, are in the same molecule. Since the reaction stops when one alcoholic hydroxyl group has reacted with the carbonyl group, the product is called a *semiacetal* or *hemiacetal*. In forming an ordinary acetal two alcoholic hydroxyl groups react with an aldehyde group (see page 75).

The conversion of the open chain (aldehyde form) into a ring or cyclic structure (semiacetal form) renders the aldehyde carbon atom asymmetric and thereby increases the number of possible isomers. The semiacetals are known as  $\alpha$  and  $\beta$  forms of the sugar. They are isomeric forms, but they are not mirror images of each other. The semiacetal having the highest positive rotation is referred to as the  $\alpha$ -compound. In the  $\alpha$ -compound the hydroxyl group attached to the aldehydic carbon atom and the hydroxyl group on the adjacent carbon atom are on the same side of the ring (*cis* positions). In the  $\beta$ -form these hydroxyl groups are on opposite sides of the semiacetal ring (*trans* positions).

For many years the  $\alpha$ - and  $\beta$ -sugars and their derivatives were represented as butylene oxides ( $\gamma$ -semiacetals). There is evidence now that in many of them, ring closure is effected through the  $\delta$ -carbon atom.\*

In solution the three forms of a monosaccharide are in equilibrium with each other, but the equilibrium is established with practically all of the sugar in the semiacetal form. In the solid state the monosaccharides are probably in semiacetal forms exclusively. The ring structures are more accurately represented as follows: †

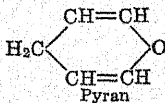
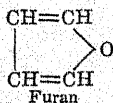


To visualize these structures think of the carbon atoms as being in a plane perpendicular to the plane of the paper. Then the atoms or groups shown above the carbon atoms are above the plane of the ring and those placed below the carbon atoms are on the opposite side of this plane.

Through a reversal of the process of semiacetal formation either of these sugars may revert to the aldehyde form. The hydrogen atom marked with a star is able to shift its position from one to the other of the two oxygen atoms. This capacity of a hydrogen atom to occupy either of two positions accounts for

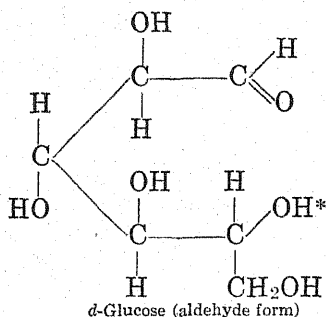
\* For a full discussion of the structures of the sugars see W. N. Haworth's "Constitution of Sugars." Edward Arnold and Co., London, 1929.

† These cyclic structures are often referred to as pyranose and furanose rings to indicate their relationships to pyran and furan respectively. Furan and pyran are cyclic compounds corresponding to the following formulas:



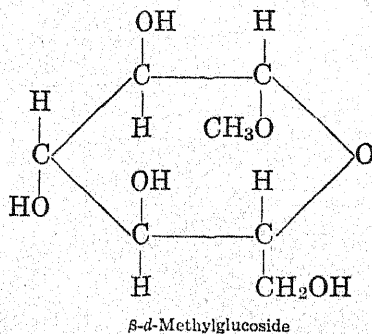
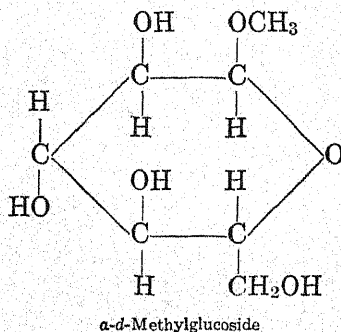
Furan (furfuran) is a colorless liquid. It boils at  $32^\circ$  and is insoluble in water. Pyran has not been isolated in the free state, but many derivatives of the compound are known.

the phenomenon of mutarotation and at the same time accounts for the aldehydic or ketonic properties of the monosaccharides.



**$\gamma$ -Sugars.** Some of the simple sugars and glucosides exist in forms that are not accounted for by assuming the existence of  $\alpha$  and  $\beta$  isomers. They are additional isomers in which the semi-acetal ring is formed through hydroxyl groups in other positions. They are designated  $\gamma$ -sugars. The term is not used to imply that the  $\gamma$ -carbon atom is engaged in the ring formation, although this is often the case. The  $\gamma$ -sugars have not been isolated, but ethers and esters derived from them are known.

**Methylglucosides.** When a solution of glucose in cold methyl alcohol is saturated with hydrogen chloride and allowed to stand several hours,  $\alpha$ - and  $\beta$ -methylglucosides are formed. These compounds have no aldehydic properties and do not display mutarotation. They are derivatives of the  $\alpha$  and  $\beta$  forms of the sugar in which methyl groups have replaced the labile hydrogen atoms. A methyl group, unlike a hydrogen atom, fails to move from one position to another. The methylglucosides, therefore, have the following permanent structures:



The methylglucosides are crystalline compounds. They may be separated by fractional crystallization or through the agency of enzymes. The enzymes *maltase* and *emulsin* act selectively upon the glucosides, the former hydrolyzing  $\alpha$ -glucosides only and the latter acting only upon the isomeric  $\beta$ -compounds.  $\alpha$ -Methylglucoside melts at  $165^\circ$  and has a specific rotation of  $+157^\circ$ . The  $\beta$ -compound melts at  $104^\circ$  and has a specific rotation of  $-33^\circ$ .

### REACTIONS OF THE MONOSACCHARIDES

1. The complex silver-ammonia ion,  $\text{Ag}(\text{NH}_3)_2^+$ , present in Tollen's reagent is reduced to free silver by the monosaccharides and by some disaccharides. Sugars that respond to this test are called "reducing sugars." The silver usually plates out on the walls of the container, producing a mirror (see page 74).

2. The sugars are converted into yellow or brown resinous substances by treatment with a warm solution of sodium hydroxide or potassium hydroxide. The structure of the resin is not known, but the colored compound is believed to be a condensation product of the aldol type (see page 71).

3. The monosaccharides, and some of the more complex carbohydrates, reduce Fehling's solution.\*

4. The monosaccharides react with acid chlorides and with acid anhydrides, forming esters. If an excess of the acylating reagent is used, all the hydroxyl groups in the sugar molecule take part in the reaction (see pages 95 and 97 for the reactions of acid chlorides and acid anhydrides on compounds containing hydroxyl groups).

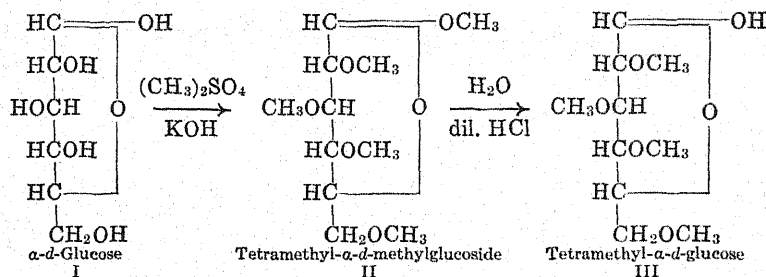
5. Dimethyl sulfate acts upon a monosaccharide, substituting a methyl group for each of the hydroxyl hydrogen atoms. With

\* Fehling's solution is prepared as follows:

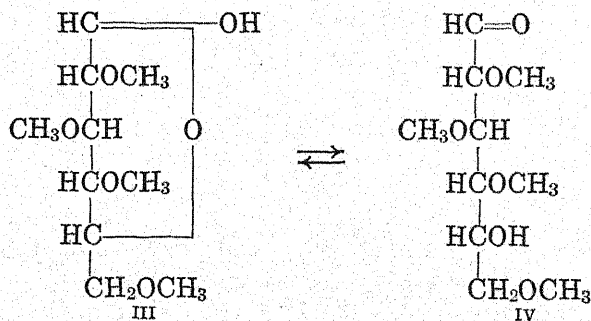
| Solution A:                         | GRAMS |
|-------------------------------------|-------|
| Water . . . . .                     | 1000  |
| Copper sulfate (hydrated) . . . . . | 69.3  |
| Solution B:                         |       |
| Water . . . . .                     | 1000  |
| Potassium hydroxide . . . . .       | 250   |
| Sodium potassium tartrate . . . . . | 346   |

For use mix equal volumes of A and B. In the presence of tartrate ions copper is not precipitated by the alkali. An aldehyde reduces copper from the cupric to the cuprous state. Cuprous oxide,  $\text{Cu}_2\text{O}$ , is precipitated. (Under some circumstances metallic copper is deposited on the walls of the vessel.) The aldehyde is oxidized to an acid. Other oxidation products are sometimes formed.

this reagent glucose yields at first a methylglucoside and finally a pentamethyl derivative. The completely methylated sugar is called tetramethyl-methylglucoside. In this compound the glucosidic methoxy group is held by a carbon atom which is attached by two valence bonds to oxygen. This group, therefore, has the characteristics of an ester and is easily hydrolyzed. The other four methyl groups are in ether-like structures and are not hydrolyzed unless very drastic treatment is applied.

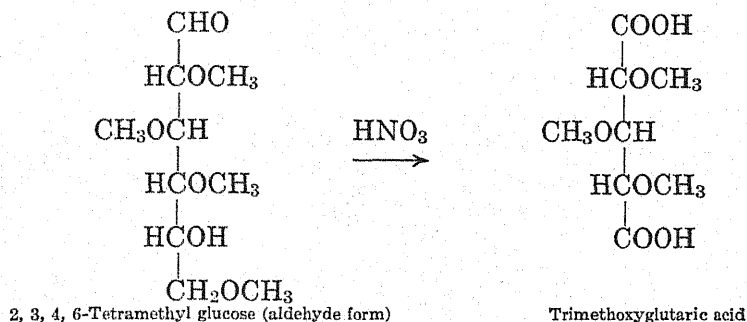


In solution the semiacetal form of the methylated sugar, tetramethyl- $\alpha$ -*d*-glucose, is in equilibrium with the aldehyde form.

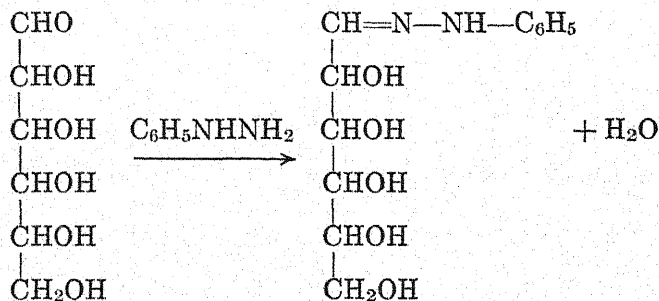


The unsubstituted hydroxyl group in formula IV marks the position at which the ring in the original glucoside, II, was closed, and presumably the free sugar, I, from which the glucoside was derived had the corresponding ring structure. This position can be determined experimentally, for the group HCOH is readily oxidized, whereas the substituted groups, HCOCH<sub>3</sub>, resist oxidation. We are, therefore, able to determine whether a given glucoside is a derivative of a  $\gamma$ -semiacetal or of a  $\delta$ -semiacetal or whether the ring was closed in some other

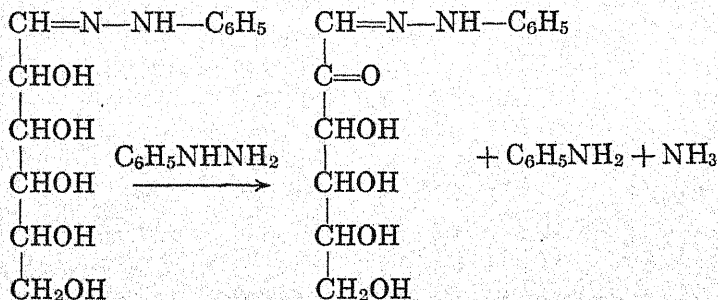
position. Treatment with nitric acid converts tetramethyl glucose into trimethoxyglutaric acid, indicating, in this case, that the original sugar was a  $\delta$ -semiacetal.



6. The monosaccharides react with phenylhydrazine forming crystalline derivatives called osazones. The first step in the process is the production of a hydrazone.

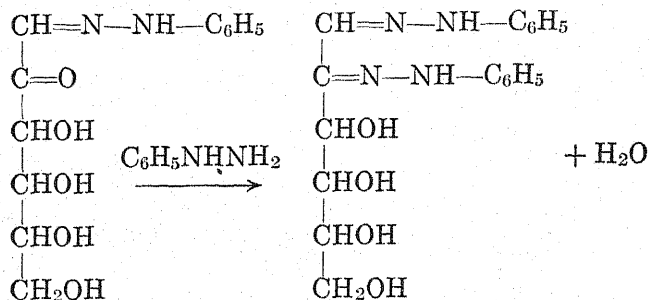


In the presence of an excess of the reagent the hydrazone is oxidized to a ketohydrazone and a molecule of phenylhydrazine is reduced, simultaneously, to aniline and ammonia :



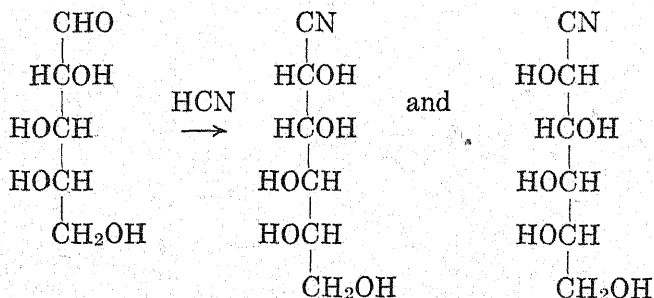


A third molecule of phenylhydrazine then acts upon this ketone, with the production of a yellow crystalline osazone:



The colors, crystal forms, and melting points of the osazones afford satisfactory means of identifying some of the sugars.

7. With hydrogen cyanide the simple sugars form addition products known as cyanhydrins. Through this reaction the carbon chain is lengthened and, at the same time, the carbon atom of the carbonyl group of the sugar is rendered asymmetric.

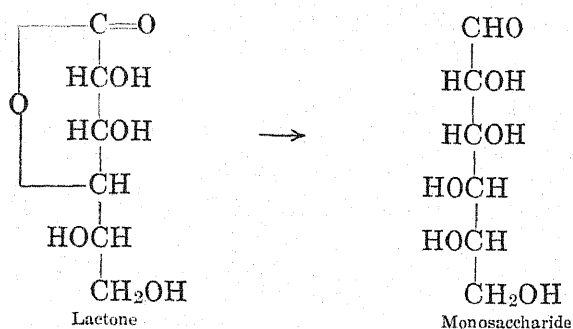


The cyanhydrins may be hydrolyzed by boiling them with hydrochloric acid, and the resulting carboxylic acids form lactones spontaneously if it is structurally possible to engage the  $\gamma$ - or the  $\delta$ - carbon atom in ring closure (that is, if there is a hydroxyl group attached to a carbon atom in either the  $\gamma$ - or the  $\delta$ - position. See page 112).

The lactones can be reduced to aldehydes by treatment with sodium amalgam and dilute sulfuric acid, or by hydrogen gas in the presence of finely divided platinum.\* Acids that do not form lactones cannot be reduced to aldehydes by these methods.

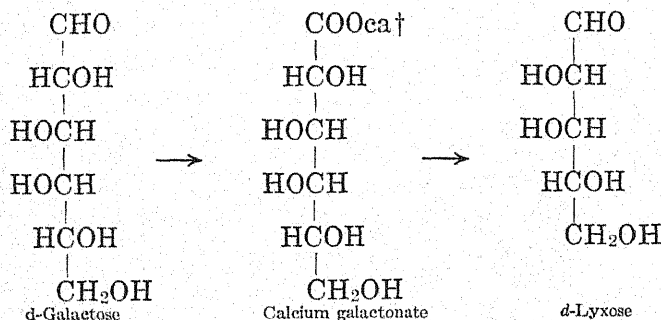
\* J. W. E. Glattfeld and G. Weber, *J. Am. Chem. Soc.*, 57, 2204 (1935).

Salts of carboxylic acids likewise resist reduction. Sulfuric acid is used with sodium amalgam to prevent the neutralization of the carboxylic acid and to favor lactone formation.



This series of reactions, aldose  $\rightarrow$  cyanhydrin  $\rightarrow$  acid  $\rightarrow$  lactone  $\rightarrow$  aldose, is known as the cyanhydrin synthesis of the monosaccharides. It is used to produce pentoses from tetroses, hexoses from pentoses, and so on.

8. It is possible also to reduce the number of carbon atoms in an aldose carbon chain. One of the best methods for accomplishing this is to oxidize the aldose to a carboxylic acid, form the calcium salt of the acid, then decompose the salt by treatment with hydrogen peroxide in the presence of ferric ions. As an example of this series of reactions we have the conversion of *d*-galactose to *d*-lyxose.\*

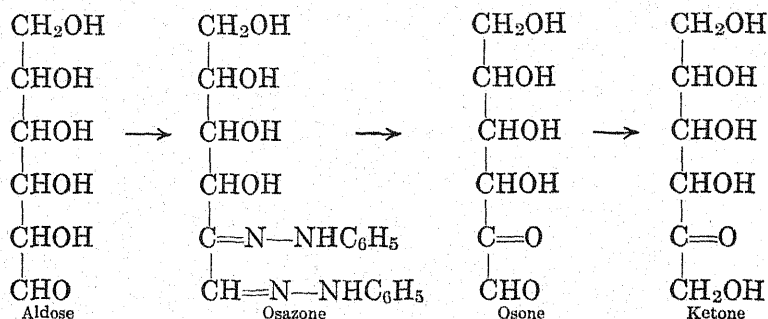


The reaction is usually carried out in a slightly acid solution and carbon dioxide is evolved.

\* Ruff and Ollendorf, *Ber.*, 33, 1798 (1900).

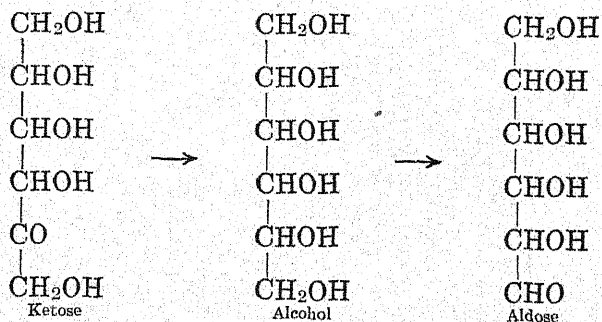
† The symbol ca stands for  $\frac{1}{2}$  Ca. It is used to avoid the necessity of writing a formula consisting of two galactose residues attached to a calcium atom.

9. Aldoses may be converted into the corresponding ketoses by the following steps: (1) by the action of phenylhydrazine an osazone is formed; (2) concentrated hydrochloric acid removes from the osazone both hydrazine groups and produces an osone; (3) the osone is reduced by zinc and acetic acid to a ketose. The third step is possible because an aldehyde is more easily reduced or oxidized than is a ketone. In the osone we have a ketone-aldehyde, and gentle reduction changes the aldehyde group only.

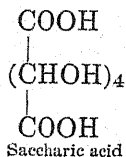
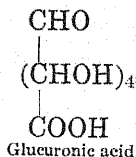
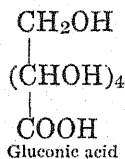


By this method fructose has been obtained from glucose. ✓

10. Ketoses may be converted into aldoses. Aldoses and ketoses are reduced by sodium amalgam to hexahydric alcohols. The terminal primary groups in these alcohols are more easily oxidized than the secondary groups, and by selective oxidation the polyhydric alcohols may be converted into aldoses. In this manner glucose has been obtained from fructose.



At the same time products of more complete oxidation are formed. Glucose, for example, yields gluconic, glucuronic, and saccharic acids:



Either gluconic acid or saccharic acid may be made to predominate in the mixture by suitable choice of oxidizing agent and proper control of the temperature. In either case a small quantity of glucuronic acid is produced.

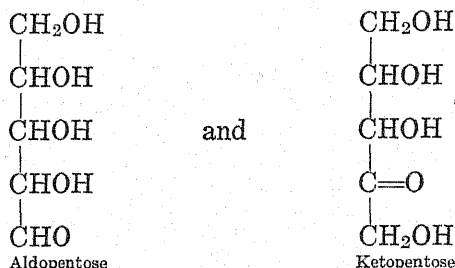
Glucuronic acid is formed by the oxidation of glucose in the living cells of the animal organism, and from the standpoint of physiological chemistry it is a product of importance. The ordinary process of carbohydrate metabolism results in the oxidation of glucose to carbon dioxide and water; but with certain substances, which are not easily oxidized in the body, glucose forms stable compounds known as glucosides. The aldehyde group of the glucose molecule is involved in the formation of the glucoside. The primary alcohol group at the opposite end of the glucose molecule is then oxidized to carboxyl, and the glucoside becomes a derivative of glucuronic acid. These derivatives of glucuronic acid are eliminated from the system in the urine. It is nature's way of removing from the animal organism such foreign substances as phenol, aniline, chloral, camphor, pinene, and many other compounds.

### CONFIGURATIONS OF THE MONOSACCHARIDES

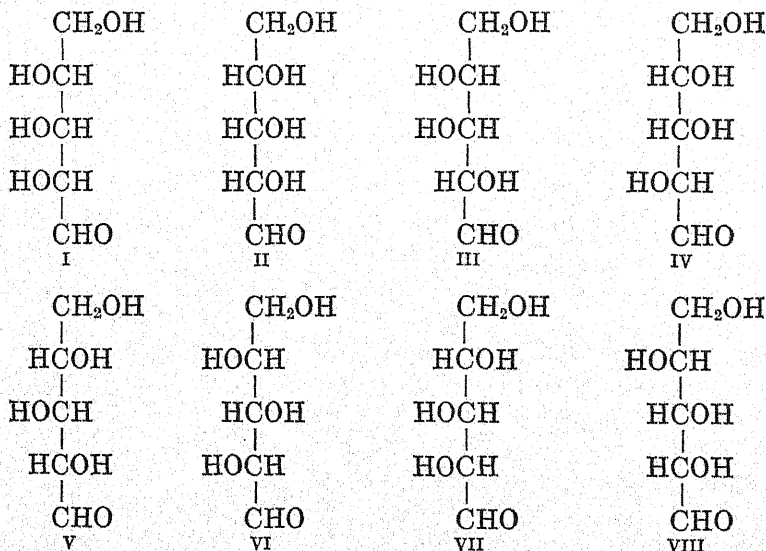
An accurate and complete structural formula of a monosaccharide must show how the groups are arranged in space around each asymmetric atom. In order to assign definite positions to the atoms and groups in the hexose molecules we must first obtain the structures of the simpler pentoses. The pentoses as well as the hexoses exist, primarily, in the form of ring compounds — cyclic structures as shown on pages 154 and 155. In determining the orientations of the hydrogen and hydroxyl groups, however, it is simpler to use the open-chain formulas. Temporarily, therefore, we shall represent the sugars as free aldehydes and ketones.

**The pentoses.** The molecular formula for any pentose is  $\text{C}_5\text{H}_{10}\text{O}_5$ . As in the case of the hexoses, these sugars are aldehyde alcohols or ketone alcohols, capable of being reduced to normal

hydrocarbons. Acetyl chloride reacts with them to form tetraacetyl derivatives. Hydrocyanic acid, hydroxylamine, and phenylhydrazine form cyanhydrins, oximes, and osazones, respectively, with the pentoses, just as they do with the hexoses. They have the structures



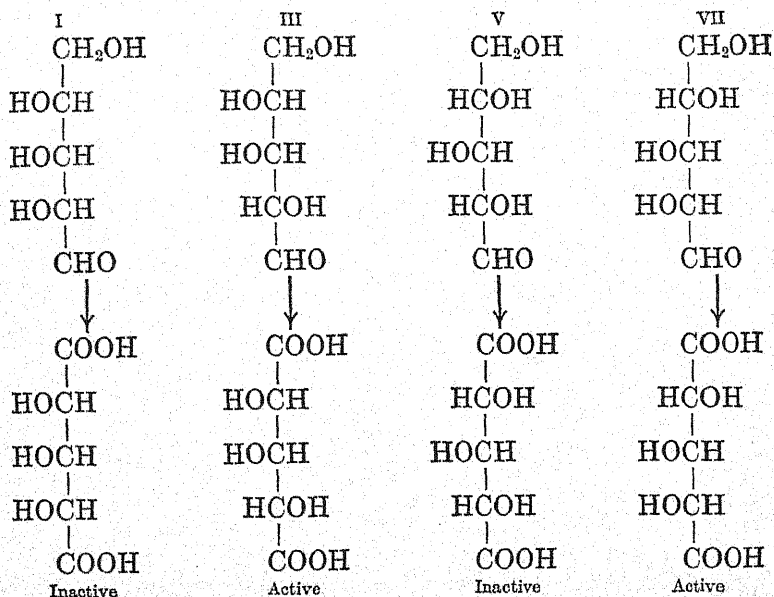
There are eight isomeric aldopentoses and four ketopentoses corresponding to these structures. Half of them are dextro-rotatory; the others are lævorotatory. The aldopentoses exist in four pairs and the ketopentoses in two pairs, each pair consisting of sugars having identical properties, except with respect to the rotation of the plane of polarization of light, and differing in this respect only in the sign of the angle of rotation. According to the structure theory four, and only four, such pairs can exist for the aldopentoses, as follows:



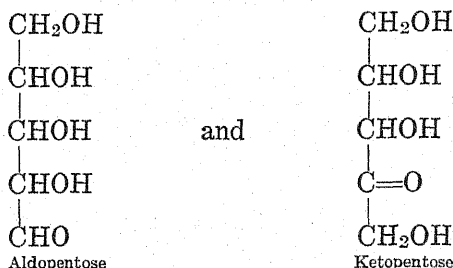
The eight aldopentoses are known as *d*- and *l*-ribose, *d*- and *l*-xylose, *d*- and *l*-arabinose, and *d*- and *l*-lyxose. It is beyond the scope of this course to consider the evidences that may ultimately enable us to specify the member of each pair that is dextrorotatory. We shall undertake merely to determine which pair of formulas should be assigned to the two arabinoses and which to the riboses, and so on. To simplify the procedure we shall keep in mind only one structure from each pair, — say, formulas I, III, V, and VII.

Arabinose and ribose react with phenylhydrazine to yield the same osazone. In forming an osazone from any aldehyde alcohol or ketone alcohol only the carbon atom of the carbonyl group and one adjacent to it become attached to phenylhydrazine residues. Hence arabinose and ribose differ from each other only in the orientation of the groups attached to the carbon atom next to the aldehyde group. They are, therefore, either I and III or V and VII.

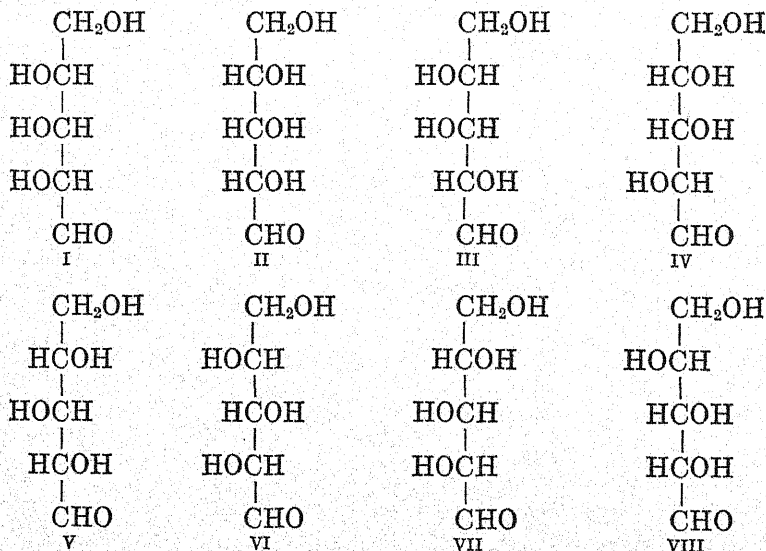
On oxidation, arabinose and lyxose yield trihydroxyglutaric acids which are optically active; ribose and xylose yield inactive trihydroxyglutaric acids. The acids derived from I and V are inactive on account of intramolecular compensation (see page 132), whereas the acids derived from III and VII are active:



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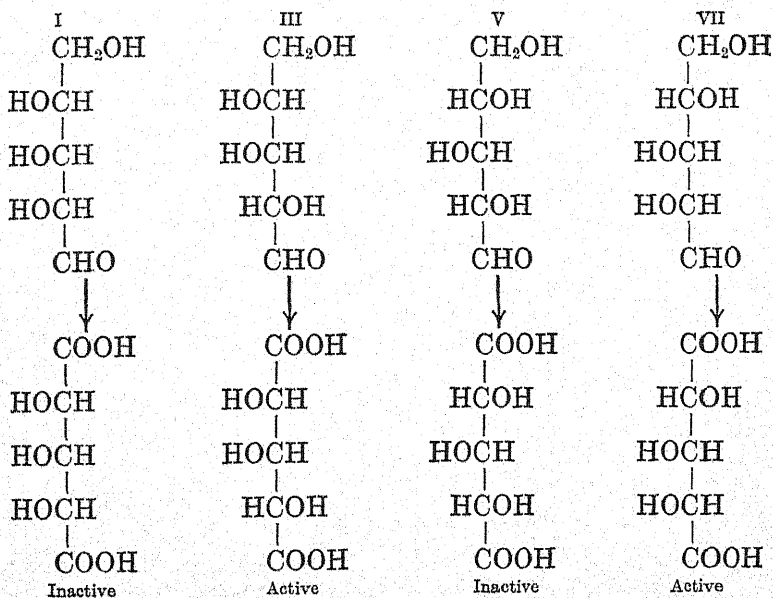
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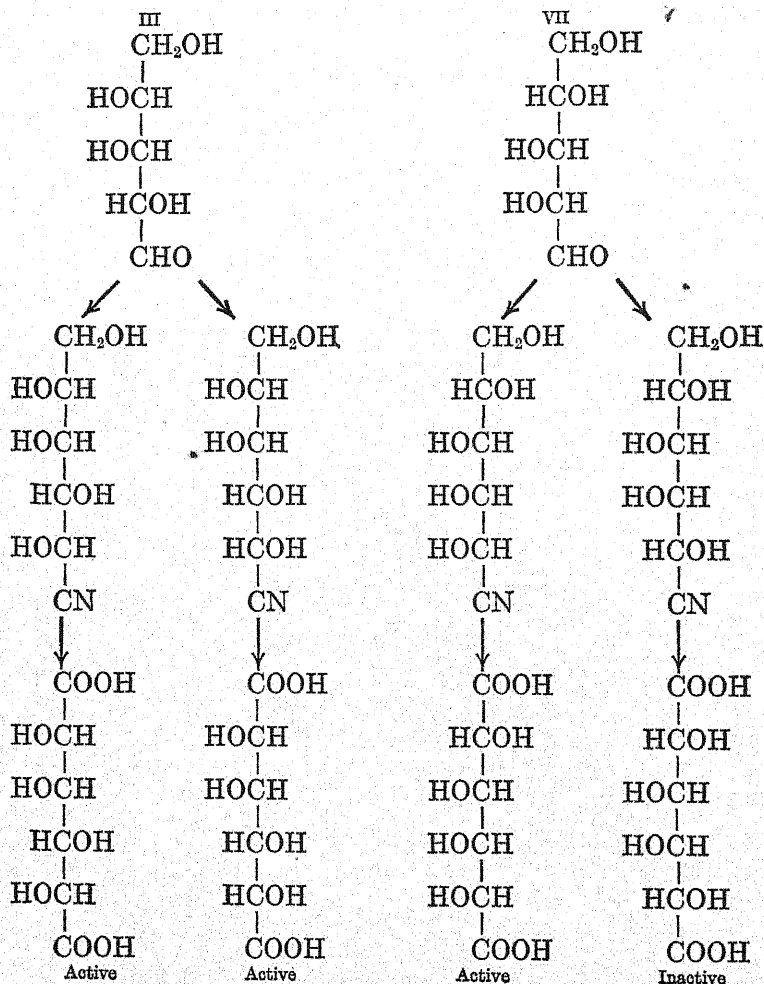
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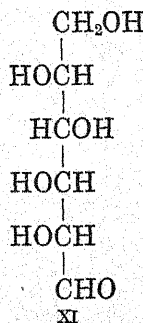
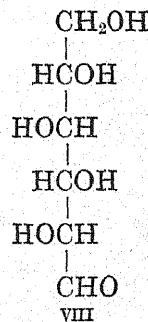
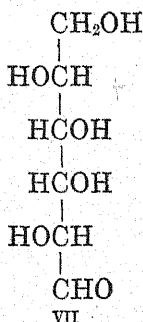
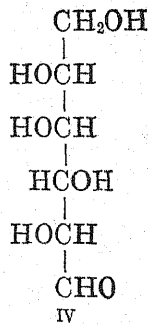
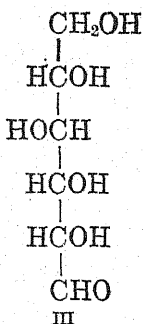
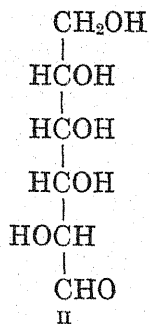
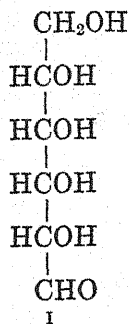
Then arabinose and lyxose are represented by formulas III and VII, but it still remains to be determined which of the two structures should be assigned to either of them. Similarly, ribose is I or V, and xylose is either I or V.

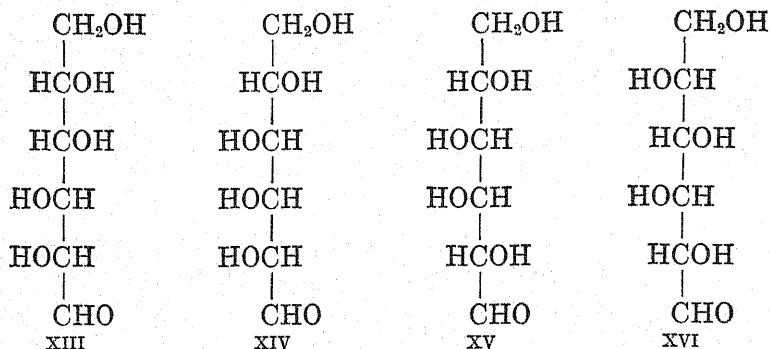
The question as to whether arabinose is III or VII is settled by treating arabinose with hydrogen cyanide, hydrolyzing the cyanhydrin, and oxidizing the resulting product to a dibasic acid. Under this treatment arabinose yields two different (isomeric) optically active dicarboxylic acids. Lyxose under similar treatment yields one active and one inactive dicarboxylic acid.



Arabinose is thus proved to have formula III and lyxose VII. It follows from this conclusion that ribose is I, for arabinose and ribose yield the same osazone. It follows also that xylose is V, for lyxose and xylose form identical osazones.

**Hexoses.** The sixteen possible stereochemical formulas of the aldohexoses are given in the following table :

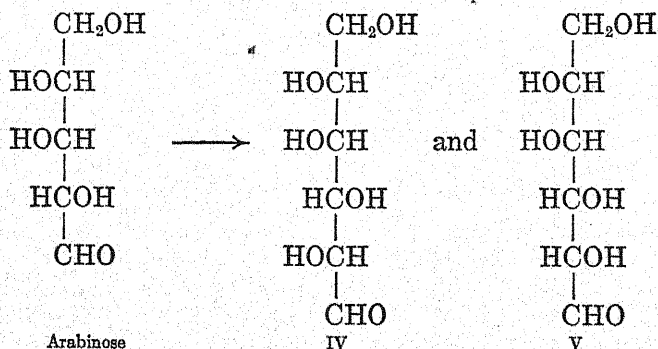




Formulas IX to XVI are mirror images of formulas I to VIII. We may, therefore, confine our attention to the first eight.

By means of the cyanhydrin synthesis\* the carbon chain in an aldose may be lengthened. Hydrocyanic acid forms an addition product with the aldehyde, thus introducing a new carbon atom, and at the same time rendering the carbon atom of the original aldehyde group asymmetric. The cyanhydrin thus formed is hydrolyzed to produce the corresponding acid. The  $\gamma$ - and  $\delta$ -hydroxy acids form lactones which can be reduced to aldehydes by treatment with sodium amalgam and dilute sulfuric acid. The presence of sulfuric acid prevents the neutralization of the carboxyl group and favors lactone formation. Salts of these acids are not reduced to aldehydes. Free carboxylic acids that are not able to pass into the lactone form likewise resist the action of sodium amalgam.

By the cyanhydrin synthesis arabinose is converted into a mixture of glucose and mannose:



\* Kiliani, *Ber.*, 18, 3066 (1885); *ibid.* 19, 221 (1886).

Glucose is, therefore, either IV or V, and mannose is the other member of this pair.

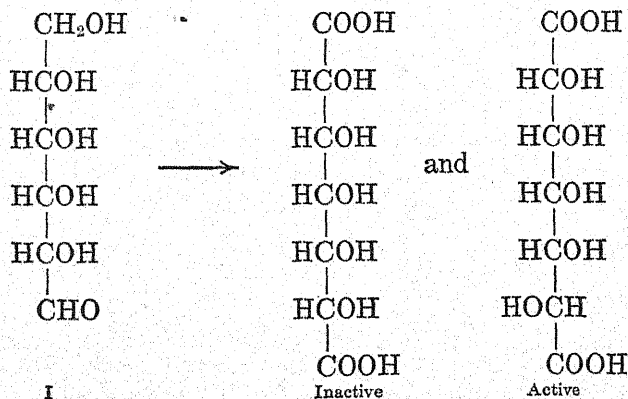
Glucose and gulose, when oxidized, yield the same dicarboxylic acid. Hence it is evident that a transposition of the aldehyde and primary alcohol groups in glucose would result in the formation of gulose. Transposing these groups in formula V would not change the structure of the molecule. The same transposition in IV would produce a different sugar. Formula IV, therefore, must be assigned to glucose, and V represents the structure of mannose.

Glucose and gulose yield the same dicarboxylic acid on oxidation. Gulose, therefore, has the structure represented by formula III.

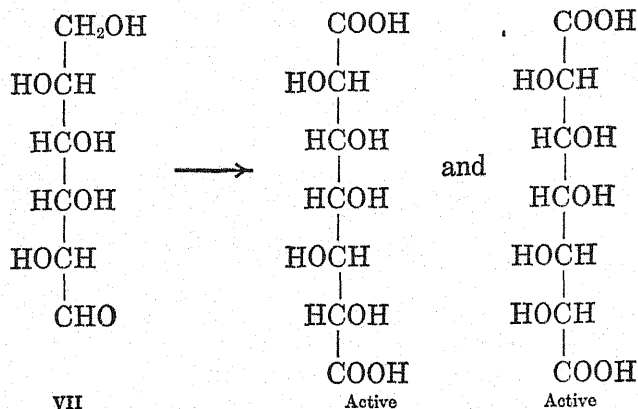
Idose and gulose yield the same osazone. This relationship indicates that they differ only in the asymmetry of the carbon next to the carbonyl group. We have proved that gulose has formula III; hence idose has formula VIII.

Galactose, an aldohexose obtained from the hydrolysis products of milk sugar, yields optically inactive products when oxidized to a dicarboxylic acid or reduced to a hexahydric alcohol. Of the four structures still unassigned only I and VII would be converted into inactive products by making the terminal groups alike. Galactose, therefore, is I or VII.

By introducing an additional carbon atom into the galactose molecule by means of hydrocyanic acid, hydrolyzing the cyanhydrin, and oxidizing this product, we obtain two active dicarboxylic acids (pentahydroxypimelic acids). Formula I gives rise to one active and one inactive product:



From VII two active products are obtained, as indicated below :

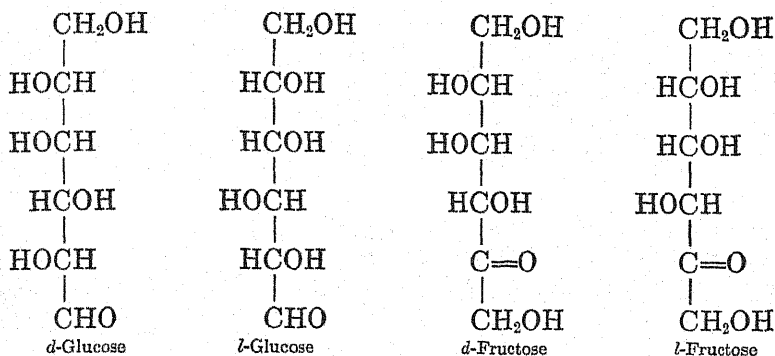


The galactose formula, therefore, is VII; and since galactose and talose yield the same osazone, talose must have formula VI.

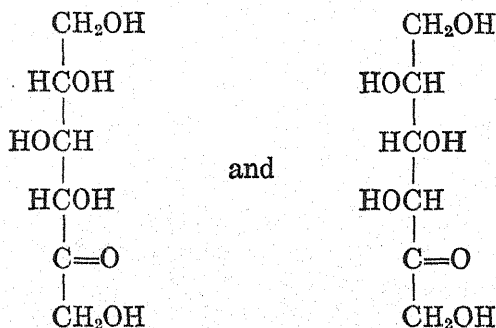
By the cyanhydrin synthesis ribose yields two hexoses having formulas I and II. They are called allose and altrose respectively. Altrose and talose, when oxidized, yield the same dicarboxylic acid. Altrose, therefore, corresponds to formula II, and allose is represented by formula I.

Assuming that formulas I to VIII represent the dextro-rotatory forms of the sugars, their mirror images (IX to XVI) must be assigned to the corresponding lævorotatory compounds. We shall not undertake to determine which formula in each pair actually belongs to the dextrorotatory compound.

The ketoses are readily converted into derivatives of the aldoses. By identifying these derivatives of known structure, the configurations of the ketoses may be ascertained. For example, glucose and fructose yield the same osazone. The two sugars are alike in structure, therefore, with the exception of the grouping around the carbonyl carbon atom and one adjacent to it. In the aldose the carbonyl group is terminal. This, in connection with the fact that glucose and fructose yield identical osazones, proves that the carbonyl group in fructose is adjacent to the terminal carbon. With the glucose structure known, and the identity of the osazones of glucose and fructose established, the formula of fructose may be written as follows:



Sorbose, gulose, and idose yield the same osazone, indicating that *d*-sorbose and *l*-sorbose must be represented by the structures



Emil Fischer divided the simple sugars into two general classes: (1) those possessing structures similar to the structure of *dextro*glucose and (2) those genetically related to *laevoglucose*.<sup>\*</sup> The first group is referred to as the *d* series, and the second is the *l* series. Two sugars are said to be genetically related if on oxidation they yield the same dibasic acid or if on treatment with phenylhydrazine they yield the same osazone, but these reactions are not the only criteria for placing a sugar in a particular series. Any compound is genetically related to its derivatives and to the compounds from which it can be made. Dextrose is a dextrorotatory aldose, and *laevulose* is a *laevo*-rotatory ketose; but they react with phenylhydrazine to form identical osazones. The structures of the two sugars are alike in so far as the asymmetric groups are concerned, and the official name of the *laevo*rotatory ketose is *d*-fructose. From

<sup>\*</sup> Fischer, *Ber.*, 24, 1836, 2683 (1891); *ibid.*, 27, 3208 (1894).

*d*-glucose we obtain by oxidation *d*-gluconic acid and *d*-saccharic acid, and from *l*-glucose we obtain, in the same way, *l*-gluconic acid and *l*-saccharic acid. In these names, *d* and *l* have no reference to optical activity. They indicate structural relationships to *d*-glucose and *l*-glucose respectively.

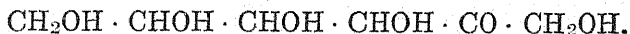
It is unfortunate that the same symbols have been chosen to represent entirely different things. Many plans have been made to change this condition, but it is difficult to modify an established custom. Rosanoff proposed the use of the Greek letters  $\delta$  and  $\lambda$  to designate the two series of sugars and their derivatives so that the English letters *d* and *l* could be used exclusively to indicate the optical properties of the compounds. According to his plan the sugar we now call *d*-fructose would be called *l*- $\delta$ -fructose, the *l* denoting lævorotation and the  $\delta$  indicating a structural relationship to dextroglucose. Others advise the use of the letters *d* and *l* to indicate structural relationships and the use of the words *dextro* and *lævo* to indicate directions of optical rotation.

*Dextrose* (*d*-glucose or *grape sugar*), a colorless, crystalline sugar, is present in most fruits, either in the free state or as a constituent of polysaccharides. It is obtained with an equivalent amount of *d*-fructose when cane sugar is hydrolyzed. It is the ultimate hydrolysis product of starch and glycogen. It is made from corn starch by treatment with hot dilute hydrochloric acid. Dextrose occurs in the blood, normally, to the extent of one tenth of one per cent. In persons suffering with diabetes the glucose content of the blood may be as high as 1.2 per cent. The sugar crystallizes from water in hexagonal plates, containing one molecule of water and melting at 86°. From alcohol it crystallizes in anhydrous needles, melting at 146°. It is dextrorotatory ( $[\alpha]_D = +52.7^\circ$ ). The  $\alpha$  and  $\beta$  forms of this sugar have been described (see page 154). Dextrose reduces Fehling's solution, yielding a precipitate of cuprous oxide.

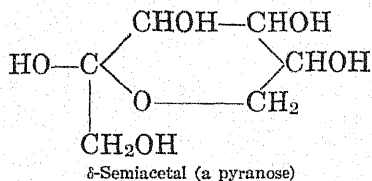
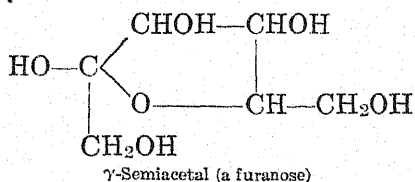
*Levulose* (*d*-fructose or *fruit sugar*) occurs combined with *d*-glucose in cane and beet sugar, and exists in the free state mixed with glucose and other substances in honey. It is the sole product obtained when inulin, a starchlike polysaccharide found in many plants, is hydrolyzed. It crystallizes in rhombic needles, melting at 104°. It is lævorotatory ( $[\alpha]_D = -93^\circ$ ).

Like glucose, fructose has the empirical formula  $C_6H_{12}O_6$ . It yields a penta-acetyl derivative, an oxime, and an osazone.

The latter is identical with the product formed by the action of glucose on phenylhydrazine. Hence the structure of fructose differs from that of dextrose only in the orientation of groups attached to terminal and penultimate carbon atoms. Unlike glucose, it fails to yield an acid with the same carbon content when oxidized, but gives rise to two acids of lower molecular weight, namely, glycolic acid and trihydroxybutyric acid. It is therefore a ketone having the formula



The ketoses, like the aldoses, exist primarily in the form of semiacetals. The semiacetal may be formed through a reaction of the carbonyl group with a hydroxyl group on either the  $\gamma$ - or the  $\delta$ -carbon atom, and the structure of the fructose molecule is represented by one of the following formulas:



There is evidence to support the conclusion that fructose in the free state exists in the form of the six-membered ring (*pyranose* structure) but as a component of the cane sugar molecule it exists in the form of a five-membered ring (*furanose* structure). When sucrose is hydrolyzed the fructose half of the molecule changes from a five-membered ring to a six-membered ring.

*d-Mannose*,  $\text{C}_6\text{H}_{12}\text{O}_6$ , is a constituent of a great variety of glucosides, but apparently does not exist in the free state as a natural product. It resembles glucose in general physical and chemical properties. With phenylhydrazine it yields a yellow



crystalline osazone, identical with the osazones from glucose and fructose. It is an aldose differing from *d*-glucose only in the orientation of the hydrogen and hydroxyl groups attached to the  $\alpha$ -carbon atom (that is, the carbon atom next to the aldehyde group). Mannose is an amorphous, colorless solid. It dissolves readily in water.

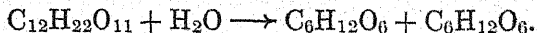
*d*-Galactose,  $C_6H_{12}O_6$ , is obtained, with an equal amount of *d*-glucose, by hydrolyzing milk sugar. It is an aldohexose, dextrorotatory, and fermentable, under the influence of an enzyme occurring in some yeasts. Nitric acid converts it into mucic acid,  $COOH \cdot (CHOH)_4 \cdot COOH$ .

Galactose is produced in sugar beets under unfavorable conditions of growth. It combines with sucrose in the beet, forming a trisaccharide, raffinose. Drought, frost, or any other factor that disturbs the normal development of the plant increases the yield of raffinose.

Galactose crystals melt at  $168^\circ$ . The sugar is strongly dextrorotatory ( $[\alpha]_D = +81.5^\circ$ ).

### THE DISACCHARIDES

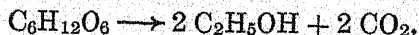
The most important disaccharides have the empirical formula  $C_{12}H_{22}O_{11}$  and yield hexoses when hydrolyzed:



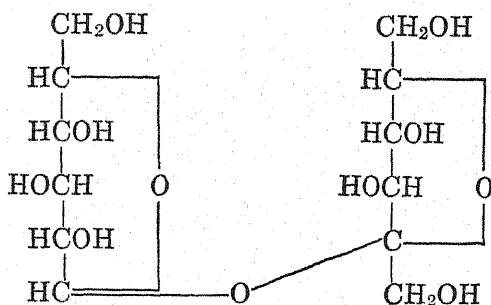
The two hexose molecules may be alike or different.

*Sucrose*,  $C_{12}H_{22}O_{11}$ , commonly called cane sugar, is obtained from sugar beets and from cane. It is present in considerable quantities in the sap of many trees, including palms, birches, and the sugar maple. Flowers (the sources of honey) and ripe fruits are also natural repositories of this sugar.

An enzyme, invertase, found in many yeasts and molds, catalyzes the hydrolysis of sucrose, the hydrolytic cleavage producing dextrose and lævulose in equal amounts. The equimolecular mixture of dextrose and lævulose (derived from dextrorotatory cane sugar) is lævorotatory, and on account of the change in the direction of rotation, the mixture is often called invert sugar. Dextrose and lævulose are both fermentable, the change being induced by enzymes found in yeast:

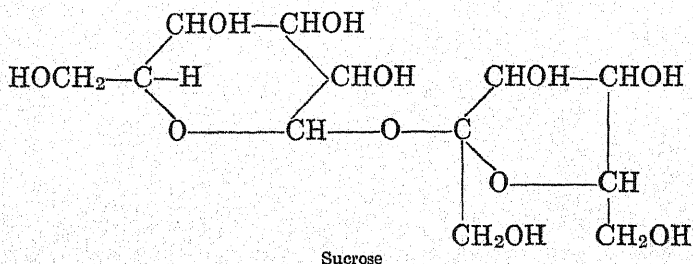


Sucrose does not respond to tests for the carbonyl group. The aldehyde group in glucose and the ketone group in fructose are altered in the establishment of the bond between these simple sugars in the sucrose molecule. Haworth has proposed the following formula for sucrose :



As shown in this formula the semiacetal rings are formed through carbon atoms 1 and 5 in the *d*-glucose unit and through carbon atoms 2 and 5 in the *d*-fructose half of the molecule. These positions were assigned by Haworth after the hydroxyl groups in sucrose had been methylated, the product hydrolyzed, and the structures of the methylated hydrolysis products had been established.\* Hudson claims, however, that the ring structures in the sugars often change during the process of methylation and that Haworth's method of determining the constitution of a disaccharide is unreliable.

To emphasize the ring structures of the glucose and fructose components of the cane sugar molecule the formula may be written as follows :



\* Haworth, Hirst, and Miller, *J. Chem. Soc.*, 1929, 2469. For a different opinion concerning the structure of cane sugar see Hudson, *J. Am. Chem. Soc.*, 52, 1707 (1930).

Cane sugar is not oxidized by Fehling's solution, and it fails to form an osazone when treated with phenylhydrazine. Sucrose is easily hydrolyzed by hot dilute acid solution but is not attacked by dilute alkalis. In this respect it resembles ordinary acetals. The specific rotation of cane sugar is  $+66.5^\circ$ .

Sugar obtained from beets, when pure, is identical with pure cane sugar, and the commercial product from either source should contain less than 1 per cent of impurities. The foreign matter retained by sugar crystals varies in character with the source. It is possible, therefore, to distinguish between crude specimens of cane and beet sugar by identifying the impurities, but impossible to detect any difference between pure samples from the two sources.

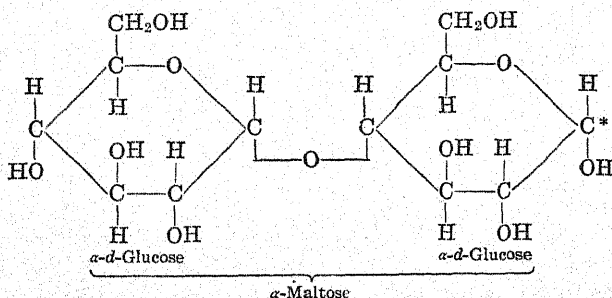
In the manufacture of sugar from beets care is exercised to avoid unnecessary rupturing of the cell walls. The beets are not crushed and pressed, but the sucrose is allowed to diffuse out of the cells of the plant tissue into water, leaving in the extracted pulp large quantities of less diffusible bitter substances that would contaminate the product if the juice were expressed from the ground or crushed material.

The beets are cleaned by scrubbing them in warm water. They are then conveyed to automatic scales, weighed, and transferred to the slicer, a mill provided with rotating blades that cut the beets in long, slender strips called cossettes. These are conveyed to the diffusion battery, which consists of twelve or more steel tanks (cells of the battery), each having a capacity of two or three tons of cossettes. A stream of hot water enters at the top of one tank, passes down through the pulp, and is forced up through a heating tube to the top of the second cell, and so on. The solution passes from one unit of the battery to another, finally emerging with a sugar content almost equal to that in the tissue fluids of freshly cut cossettes. The process is continuous. Fresh water is delivered to the tank that contains pulp, from which the sugar has been almost completely removed, and as it passes through the battery it encounters, in each succeeding cell, pulp that is richer in sugar until it finally passes through a tank containing cossettes just received from the slicer. There are always two cells of the battery out of the diffusion circuit. From one the waste pulp is being discharged, while the other is being filled with new material. The sugar solution as drawn from the diffusion battery is dark in color. It is clarified by the addition of milk of lime,  $\text{Ca(OH)}_2$ , and subsequent precipitation of the calcium as carbonate by treatment with carbon dioxide. Colloidal substances suspended in the aqueous extract are mechanically carried down with the precipitate and removed from the juice by filtration. Further purification is effected by treating the solution with sulfur dioxide and again filtering. To avoid hydrolysis of the sugar, complete neutralization

of the calcium hydroxide by sulfurous acid is carefully avoided. The clarified juice is evaporated under reduced pressure, until the sugar crystallizes, and the mother liquor is then removed by means of centrifugal filters. The sugar is dried in rotating tubes, five or six feet in diameter and twenty feet long, through which it is made to travel against a counter-current of hot air.

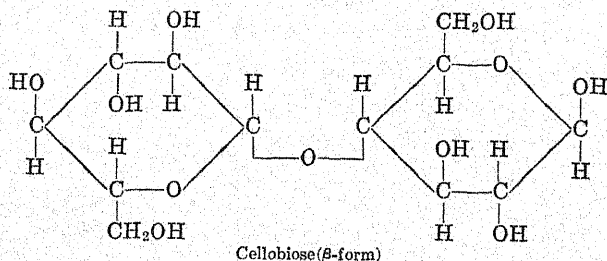
The sugar content of a solution is estimated by a determination of its optical rotation. Sucrose is strongly dextrorotatory ( $[\alpha]_D = 66.5^\circ$ ). Optically active proteins are present in the juice obtained from beets, and these have to be removed before the analysis is made. The proteins are precipitated and the solution is rendered optically clear by treatment with lead acetate. To estimate sucrose in the presence of glucose or any other monose, the optical rotation of the mixture is measured, and the solution is then boiled with hydrochloric acid to hydrolyze the disaccharide, and returned to the polarimeter for a second reading. From the change in the angle of rotation caused by substitution of invert sugar for sucrose, the quantity of the latter in the original mixture may be calculated.

*Maltose.* Under the influence of an enzyme known as diastase, which is present in sprouting barley, starch is hydrolyzed to maltose; and maltose is hydrolyzed to glucose by an enzyme, maltase, found in most yeasts. Both of these ferments are present in the fluids of the alimentary canal. Ordinary yeast contains the enzymes necessary to cause the fermentation of maltose. The fermentation products are ethyl alcohol and carbon dioxide. Maltose crystallizes from alcohol in an anhydrous form, and from aqueous solutions it crystallizes with one molecule of water. The needle-like crystals of the commercial product correspond to the formula  $C_{12}H_{22}O_{11} \cdot H_2O$ . Maltose forms an osazone with phenylhydrazine and it reduces Fehling's solution, indicating the presence of a carbonyl group. Only one aldehyde group is involved in the union of two glucose molecules when they combine to form maltose. The ordinary form of the sugar is represented by the following formula :



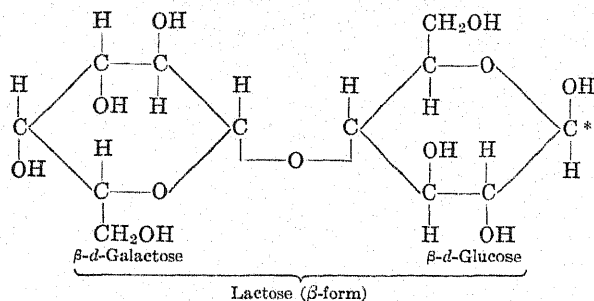
The group which is capable of functioning as an aldehyde group is marked with an asterisk. This formula represents the sugar as a glucoside. The labile hydrogen atom in one glucose molecule has been replaced by another glucose unit. We have already considered the methylglucosides — compounds formed from glucose by substituting a methyl group for the labile hydrogen atom. We found it possible to produce two stable methylglucosides corresponding in structures to the  $\alpha$ - and  $\beta$ -forms of the glucose molecule. Similarly it is possible to obtain a glucose-glucoside by substituting a glucose residue (instead of a methyl group) for the labile hydrogen atom in  $\alpha$ -glucose or in  $\beta$ -glucose. Maltose is a glucose-glucoside of this type. In ordinary maltose, which is obtained from grain, both hexose units are derived from  $\alpha$ -*D*-glucose. The carbon atom marked by an asterisk is potentially aldehydic, and a reversal of the positions of the hydrogen atom and the hydroxyl group on this carbon atom is possible. This possibility is realized, as is indicated by the fact that maltose displays mutarotation. Ordinary maltose is hydrolyzed by maltase and is not hydrolyzed by emulsin. It is therefore an  $\alpha$ -glucoside (see page 157). Starch molecules consist of long chains of maltose units.

*Cellobiose*,  $C_{12}H_{22}O_{11}$ , is obtained from cellulose. Wood pulp and cotton are common sources of this sugar. Prolonged treatment with acetic anhydride and sulfuric acid converts cellulose into cellulose acetates which can be hydrolyzed to cellobiose. Emulsin acts upon cellobiose, converting it into glucose. The configuration of the cellobiose molecule ( $\beta$ -form) is represented by the following formula :



*Lactose*,  $C_{12}H_{22}O_{11}$ , is obtained from milk. The fat is separated from milk for the manufacture of butter, and the casein is precipitated by an enzyme, rennet, and is used in making

cheese. Lactose, or milk sugar, remains in the whey, from which it may be obtained by evaporating the latter to a small volume. The crystals of lactose are hard and they dissolve slowly. The solution is dextrorotatory. Lactose is not as sweet as cane sugar. It forms an osazone and reduces Fehling's solution and an ammoniacal silver solution. On hydrolysis lactose yields *d*-glucose and *d*-galactose. The  $\beta$ -form of the sugar is present in milk.



The reducing group (free aldehyde group) in lactose is in the glucose half of the molecule. The position of the group is indicated by an asterisk.

Lactose is used in the preparation of mucic acid, which is derived from the galactose half of the molecule by oxidation with nitric acid.

An enzyme produced by the lactic acid bacillus converts lactose into  $\alpha$ -hydroxypropionic acid,  $\text{CH}_3 \cdot \text{CHOH} \cdot \text{COOH}$ , commonly called lactic acid. This transformation, known as lactic fermentation, is the cause of the souring of milk. Ordinary yeast does not cause fermentation in a solution of lactose.

### POLYSACCHARIDES

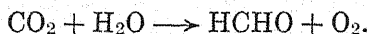
Starch, inulin, glycogen, and cellulose are typical polysaccharides. They are amorphous carbohydrates of high molecular weight, and they are almost tasteless. On hydrolysis they yield hexoses. Although many members of this group are fairly soluble in water, they do not produce appreciable lowerings in the vapor pressure of the solvent. It is impossible, therefore, to determine their molecular weights, but the values must be very high. A polysaccharide is composed of  $n$  hexose molecules less  $n - 1$  molecules of water; and if  $n$  is large, the

composition of the compound approaches the value expressed by the empirical formula  $(C_6H_{10}O_5)_n$ .

*Starch*,  $(C_6H_{10}O_5)_n$ , is present in large quantities in all plants. It is especially abundant in potatoes and other tubers, and in wheat, corn, rice, and other cereals. It occurs in the form of granules, and each source of starch yields granules of characteristic form. By microscopic examination of starch it is often possible to determine its origin.

When heated, starch is partly converted into polysaccharides of lower molecular weight, known as dextrins. When boiled with dilute acids, it is hydrolyzed to glucose. The enzyme diastase acts upon a suspension of starch in water, hydrolyzing the starch to maltose and isomaltose. In cold water starch is only slightly soluble. In hot water the granules swell, forming a paste. A highly dispersed suspension of starch particles (colloidal solution) is obtained by boiling starch with water. Starch paste is used as an indicator for free iodine. A deep blue color is produced when starch absorbs iodine.

Formaldehyde has been condensed to acrose, a sugar isomeric with glucose, and since starch is a polymer of glucose, it has been suggested that starch is formed in plant tissue by a condensation of this type. Carbon dioxide taken into the plant through the leaves, and water entering by way of the roots, furnish the components from which formaldehyde may be made:



The theory that formaldehyde is formed in the plant as the starting point in the synthesis of starches and sugars was first advanced by Baeyer.\* The theory has been supported by many investigators.† In the absence of a catalyst formaldehyde is not obtained when carbon dioxide and water are exposed to sunlight or ultraviolet light.‡ In the presence of certain contact agents the photochemical reduction of carbon dioxide occurs, but the mechanism of the reaction is still obscure.§ There is no positive proof that formaldehyde is actually an intermediate in the synthesis of starch in plants.

\* Baeyer, *Ber.*, 3, 63 (1870).

† Usher and Priestly, *Proc. Roy. Soc.*, 84, B, 101 (1911). Baly, Heilbron, and Barker, *Trans. Chem. Soc.*, 119, 1025 (1921). Moore and Webster, *Proc. Roy. Soc.*, 90, B, 168 (1918).

‡ Porter and Ramsperger, *J. Am. Chem. Soc.*, 47, 79 (1925).

§ Baly and Davies, *Proc. Roy. Soc.*, 116, 219 (1927).

*Glycogen*,  $(C_6H_{10}O_5)_n$ , a white amorphous substance, constitutes the reserve supply of carbohydrate in the animal organism. It occurs primarily in the liver, but is present also in all muscular tissue. The energy change involved in the oxidation of carbohydrates contributes largely to the maintenance of the body temperature and to the development of muscular activity. Glycogen is hydrolyzed to glucose as rapidly as the latter disappears from the blood. After a meal rich in carbohydrates, glucose reaches the blood stream more rapidly than it is required in the oxidation processes of the tissues; and by a reversal of the hydrolysis process it is converted into glycogen, which is stored in the liver and elsewhere.

*Inulin*,  $(C_6H_{10}O_5)_n$ , resembles starch in many respects, but differs from it in being fairly soluble in water and in producing no color with iodine. Inulin is found in many plants. Artichokes, dahlia tubers, and chicory roots are especially productive of this polysaccharide. It is hydrolyzed very rapidly when boiled with a dilute acid and yields *d*-fructose only.

*Cellulose* constitutes the principal building material of the cell walls in plants. It is associated with lignin, a compound of unknown structure found in the bark and wood of all trees. Cotton, linen, and paper are composed of cellulose. On hydrolysis the cellulose derived from nearly all plants yields cellobiose, a disaccharide similar to maltose. This, in turn, is converted into glucose. Cellulose derived from coffee beans and from a few other sources yields *d*-mannose. Cellulose is of great technical importance. The uses of cotton, linen, and paper are almost numberless, and in addition to its uses in an unaltered state it is the source of such preparations as nitrocellulose, guncotton, collodion, and artificial silk.

*Rayon*. Several commercial processes have been developed for the manufacture of rayon, or artificial silk. In the viscose process cotton or wood pulp is warmed with a concentrated solution of sodium hydroxide to form a compound (or a mixture of several compounds) known as alkali cellulose. This product is converted into sodium cellulose xanthate, or *viscose*, by treatment with carbon disulfide. Viscose is an amber-colored transparent substance. After proper aging it is forced through fine holes into an acid solution, and cellulose xanthic acid is produced in the form of fine threads. This loses carbon disulfide, regenerating cellulose without change in form.



## ENZYMES

A chemical substance derived from a living cell and capable of changing the rate of a chemical reaction by contact with the reagents is called an enzyme. The enzyme itself is not destroyed in the reaction which it accelerates. It is an organic catalyst. In displaying more or less specificity of action enzymes differ, in degree at least, from inorganic catalysts. For example, an enzyme that causes the fermentation of *d*-glucose will not produce a similar change in the isomeric *l*-glucose. This fact led Fischer to assume that there must be a definite relationship between the molecular structure of the enzyme and that of the substance upon which it acts. He made the idea more definite by comparing the substrate to a lock and the enzyme that acts upon it to a key that has the proper configuration to turn the lock. Bayliss thinks this analogy has been overworked and claims that not all enzymes are specific in their catalytic effects.

Enzymes act only at moderate temperatures. At zero they are inactive, but the activity is restored when the solution is warmed. They are permanently destroyed by temperatures approaching 100° C.

One of the first cases of enzyme action to be carefully studied was that of the production of alcohol from sugar, through fermentation induced by yeast. Pasteur believed that fermentation was a result of physiological processes in the living yeast cell. He assumed that sugar was a food for the living organism and alcohol a product of carbohydrate metabolism within the cell. The production of alcohol was due, therefore, to certain biological functions of living microorganisms. This theory of fermentation was accepted until Buchner's classical experiment (1897) indicated a different cause for the process. Buchner triturated yeast with sand until all cell walls were ruptured. He extracted the mass with water and forced the solution through an unglazed porcelain filter. The filtrate was an optically clear solution containing no living cells. Incubation under optimum conditions of temperature and nutriment produced no sign of life. Yet this sterile solution of substances extracted from the living cells was found to be as potent as the yeast plant

itself in causing alcoholic fermentation of glucose. The decomposition of glucose into alcohol and carbon dioxide is accomplished under the influence of an unorganized ferment — a chemical compound — derived from the yeast cells. Buchner called this substance zymase. It is a typical enzyme. Yeast produces another enzyme, invertase, which catalyzes the hydrolysis of cane sugar. Zymase operates only on the invert sugar (*d*-glucose and *d*-fructose).

If it were not removed from the field of action, a very small quantity of an enzyme would be sufficient to change an unlimited amount of the substrate. Loss of a catalyst may be due to side reactions in which it is directly involved as a reagent, or the catalyst may be mechanically carried out of the mixture by adsorption on the surfaces of products formed in the main reaction. Invertase in a solution of cane sugar remains active until more than 200,000 times its own weight of sucrose has been hydrolyzed, and rennet is said to precipitate from milk as much as 400,000 times its weight of casein.

There are obstacles in the way of securing unambiguous results in the study of enzyme action. For example, we cannot be sure that anyone has succeeded, as yet, in isolating a chemically pure specimen of an enzyme. The ordinary criteria of purity cannot be applied to enzymes. They do not crystallize and they decompose below their melting points. Their molecular weights are unknown, for, like other colloids, they produce very slight depressions of freezing points and very low osmotic pressures, these values being very little greater than the effects that might be attributed to impurities in the samples. Pepsin and trypsin are typical protein-splitting enzymes of the alimentary tract. They respond to the ordinary tests for proteins, but the observed protein reactions may be due to adsorbed foreign substances. Similarly, invertase, an enzyme that acts upon sucrose, responds to tests for carbohydrates; but that does not justify the conclusion that pure invertase is itself a carbohydrate. Attempts to purify an enzyme often result in reducing its activity as a catalyst. This may be due to removal of a co-enzyme — a substance that works with the enzyme or establishes optimum conditions for its active operation. Pepsin, for instance, is inactive in the absence of hydrochloric acid; and the fat-splitting enzyme, lipase, of the liver is active only in the presence of bile.

Enzymes are obtained from many sources. Some are found in solution in the body fluids; as, for example, ptyalin in saliva, pepsin in gastric juice, and trypsin in pancreatic juice. Others have to be extracted with water or any suitable solvent from ground cells. Invertase and zymase are obtained from yeast in this way, and erepsin is extracted from the mucous lining of the intestine.

A few of the best-known enzymes are listed below with a tabulation of sources, the substrates upon which they act, and the products of the reactions.

| ENZYMES      | SOURCES                                     | SUBSTRATES                   | PRODUCTS                            |
|--------------|---|------------------------------|-------------------------------------|
| Ptyalin . .  | Saliva . . . . .                            | Starch, dextrin . . .        | Maltose                             |
| Amylopsin .  | Pancreatic juice . . .                      | Starch, dextrin . . .        | Maltose                             |
| Glycogenase  | Liver, muscles . . . .                      | Glycogen . . . . .           | Dextrin, maltose, glucose           |
| Inulase . .  | Fungi . . . . .                             | Inulin . . . . .             | Fructose                            |
| Lactase . .  | Intestinal mucosa . . .                     | Lactose . . . . .            | Glucose and galactose               |
| Maltase . .  | Blood serum, liver, saliva, pancreas, lymph | $\alpha$ -Glucosides . . . . | Glucose and other products          |
| Invertase .  | Intestinal mucosa, yeast                    | Sucrose, glucosides . .      | Glucose, fructose                   |
| Zymase . .   | Yeast . . . . .                             | Sugars . . . . .             | Alcohol and carbon dioxide          |
| Adenase . .  | Animal tissues . . . .                      | Adenine . . . . .            | Hypoxanthine                        |
| Emulsin . .  | Plant tissues . . . . .                     | $\beta$ -Glucosides . . . .  | Glucose, etc.                       |
| Steapsin . . | Pancreatic juice . . . .                    | Fats . . . . .               | Glycerol and fatty acids            |
| Erepsin . .  | <i>Succus entericus</i> . . . .             | Polypeptides, peptones       | Amino acids                         |
| Rennin . .   | Gastric juice, pancreas .                   | Casein . . . . .             | Paracasein                          |
| Thrombin .   | Blood . . . . .                             | Fibrinogen . . . . .         | Fibrin                              |
| Pepsin . .   | Gastric juice . . . . .                     | Proteins . . . . .           | Peptones                            |
| Trypsin . .  | Pancreatic juice . . . .                    | Proteins . . . . .           | Peptones, polypeptides, amino acids |

# AROMATIC COMPOUNDS

## HYDROCARBONS

The compounds of the aliphatic series considered in the preceding chapters were regarded as derivatives of methane. In most cases these compounds were represented as having continuous open chains of carbon atoms. Hydrocarbons having the formula  $C_nH_{2n+2}$  and their derivatives were called saturated compounds; those corresponding to the formulas  $C_nH_{2n}$ ,  $C_nH_{2n-2}$ , and  $C_nH_{2n-4}$  were said to be unsaturated. The aromatic group comprises the derivatives of benzene and some other cyclic compounds. Benzene is the first member of a series of hydrocarbons corresponding to the general formula  $C_nH_{2n-6}$ , but it does not act like a highly unsaturated compound. Its six carbon atoms form a closed chain or ring, and this cyclic structure imparts to the molecule properties that would not be predicted from a consideration of the empirical formula alone.

*Benzene.* Pure benzene is an optically clear, colorless liquid boiling at  $80.4^\circ\text{C}$ . and freezing at  $5.4^\circ$ . It has a density of 0.8799 g. per cubic centimeter at  $20^\circ\text{C}$ . It is practically insoluble in water, but dissolves in all proportions in alcohol and in ether. Benzene burns with a luminous, smoky flame, and on account of its high vapor pressure readily forms explosive mixtures with air. It is an excellent solvent for fats, waxes, and resins. Hundreds of important compounds, including the valuable aniline dyes and high explosives like picric acid and trinitrotoluene, are derived from benzene.

The main commercial source of benzene is coal tar. When coal is distilled (that is, heated out of contact with air), a variety of gaseous, liquid, and viscous tarry products are expelled. A solid residue of coke remains in the retort. The process is one of great industrial value, for coal gas is used in enormous quantities for heating and lighting purposes, while the smelters, and many other concerns operating large furnaces, are dependent upon coke for fuel.

The coal gas is separated from the liquids and tar by means of condensers, and after being freed from ammonia and hydrogen sulfide by washing with water it is conveyed to storage tanks connected with the gas mains of the city. It consists of hydrogen (45 to 50 per cent), methane (30 to 40 per cent), carbon monoxide (6 to 10 per cent), and small quantities of carbon dioxide, nitrogen, acetylene, benzene, and ethylene.

The liquid distillate separates into two layers. The upper layer consists of an aqueous solution of ammonia, ammonium carbonate, ammonium hydrosulfide, pyridine, and some other compounds. This is an important commercial source of ammonia and all ammonium salts. The lower layer consists of a heavy, dark, oily, or viscous mass known as coal tar. The tar, at one time discarded as a worthless by-product, is now prized as a valuable source of many aromatic compounds. A partial separation of its components is accomplished by fractional distillation. In the preliminary treatment it is cut into five fractions, as follows:

- |                               |                               |
|-------------------------------|-------------------------------|
| 1. Light oil, 80° to 170°     | 3. Heavy oil, 230° to 270°    |
| 2. Middle oil, 170° to 230°   | 4. Anthracene oil, above 270° |
| 5. Pitch, a semisolid residue |                               |

Each fraction is then redistilled from smaller retorts or extracted with various solvents to complete the separation.

### CONSTITUTION OF BENZENE

An analysis of benzene indicates that it consists of carbon, 92.31 per cent, and hydrogen, 7.69 per cent. The simplest formula that represents these values is  $\text{CH}$ . The molecular weight of benzene is 78 and its molecular formula is therefore  $\text{C}_6\text{H}_6$ . The saturated aliphatic hydrocarbon (hexane) having six carbon atoms has the formula  $\text{C}_6\text{H}_{14}$ . From a consideration of the empirical formula,  $\text{C}_6\text{H}_6$ , one would conclude that benzene must be a highly unsaturated compound; but as a matter of fact, it acts more like a saturated hydrocarbon. Unlike the members of the acetylene series, benzene is oxidized with great difficulty. Halogen acids, cold sulfuric acid, and concentrated alkalis do not affect it, and powerful oxidizing agents, such as hot chromic acid and potassium permanganate solutions, convert it very slowly into carbon dioxide, water, and other products. The free halogens, chlorine and bromine, react with benzene, forming either substitution products, as

with saturated hydrocarbons, or addition products. The ability to form addition products reveals the fact that benzene is actually unsaturated, although its inertness is a property not shared by the unsaturated compounds of the aliphatic series.

Dipropargyl,  $C_6H_6$ , a liquid boiling at  $85^\circ$  and isomeric with benzene, is prepared by a method which indicates that it has the following formula:  $CH : C \cdot CH_2 \cdot CH_2 \cdot C : CH$ . Its properties are in strict harmony with this structure. It is highly reactive, easily oxidized, forms addition products with halogens and with halogen acids, and yields metallic derivatives with silver and copper salts. Since benzene is fundamentally different, it cannot be represented by a structure similar to that assigned to dipropargyl.

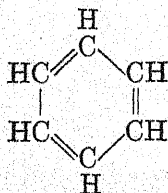
A study of the substitution products of benzene led to the conclusion that its structure must be represented as a closed chain or ring. Some of the evidences in support of this structure will be presented here, and corroborating evidence will be found in the chapters that follow.



1. There are no isomeric monosubstitution products of benzene. Only one bromobenzene, for example, is known. This is not due to a unique position in the molecule of a single hydrogen atom, making substitution take place in one position only, for all the hydrogen atoms in benzene are replaceable by the same reagent. Only one conclusion can be drawn from this fact, namely, the six hydrogen atoms in the benzene molecule are similarly placed. In other words, the molecule has a symmetrical structure, with the hydrogen atoms uniformly and equally distributed. This implies the necessity of having one and only one hydrogen atom attached to each carbon atom.

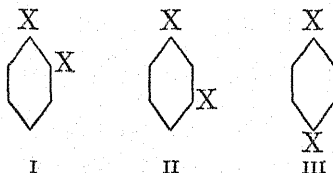
2. There are three isomeric disubstitution products of benzene, whether the substituents are alike or different.

3. There are three trisubstitution products of benzene if the substituents are alike; six if two are alike and one different; ten isomers if the three substituents are all different.

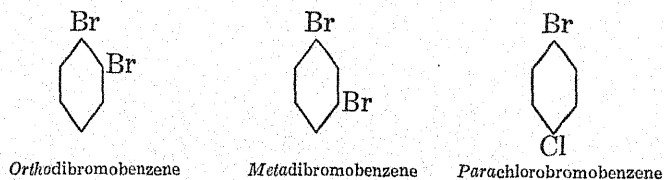
In 1864 Kekulé proposed the following structure to account for the properties enumerated in the last three paragraphs:



The benzene molecule is thus represented as a symmetrical ring or hexagon, with the carbon atoms all alike with respect to positions within the ring, and the hydrogen atoms all similarly located. To determine whether this formula accounts for the substitution products of benzene, let us economize space by writing a hexagon for the formula. The symbol  will be understood to mean  $C_6H_6$ , the six carbon and six hydrogen atoms being combined as indicated in the Kekulé formula. Similarly  Br will stand for  $C_6H_5Br$ , a substitution product derived from benzene by replacing one hydrogen atom by a bromine atom. Using the letter X to represent any atom or radical, we may represent the three disubstitution products of benzene by the following formulas:

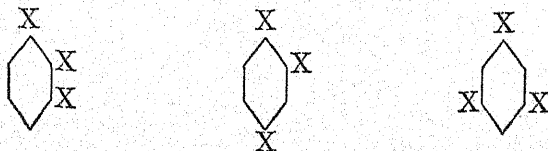


The relative positions of the substituents in formulas I, II, and III are known as *ortho*, *meta*, and *para* respectively. We specify the positions of atoms or groups in the ring as follows:

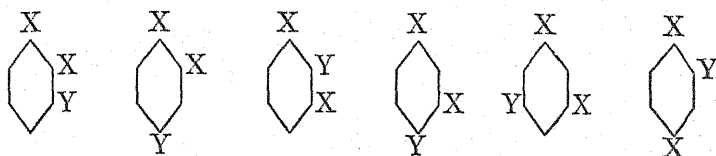


Obviously it is immaterial whether the two substituents are alike or different; the possible number of isomers remains the same in either case.

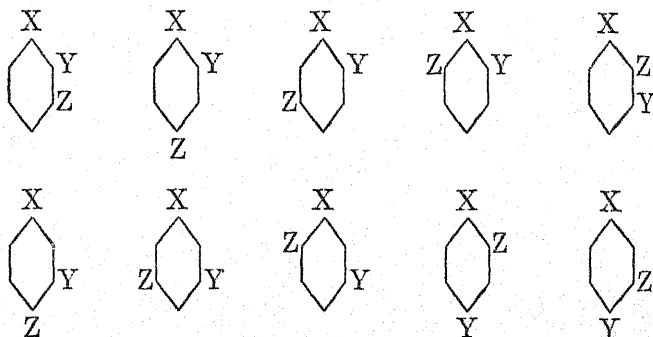
The three possible trisubstitution products, if the substituents are all alike, are represented as follows:



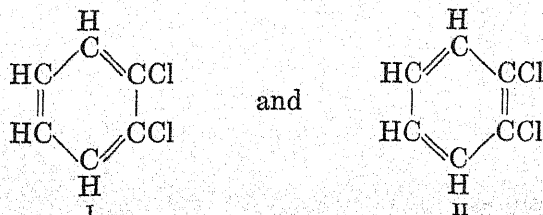
The ring structure accounts for six trisubstitution products if two of the substituents are alike :



The formula accounts also for the existence of ten isomeric products if the three substituents are different :



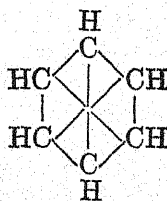
The agreement between the known number of isomers and the number that would be predicted on the basis of a ring structure gave strong support to the views expressed by Kekulé. Not all the possible compounds have actually been prepared, but in no instance has the ring structure been inadequate to account for known derivatives of benzene. But Kekulé's formula is not entirely satisfactory. This structure should give rise to isomeric *ortho* disubstitution products; for in one case the entering atoms or radicals might attach to carbon atoms held together by a single bond, and in the other case to carbon atoms held by a double bond. Thus there should be two *orthodichlorobenzenes* :





No such isomers exist, or, at any rate, no substantial chemical evidence of their existence has been found up to the present time.\* Kekulé met this objection with the assumption that the double bonds are constantly shifting positions. He maintained that the formula as written above represents a dynamic rather than a static relationship between the atoms. Half the molecules of *orthodichlorobenzene* correspond to formula I and half to formula II, or, in other words, any particular molecule is in the condition represented by formula I half of the time and in the other form half of the time. This ingenious explanation has never fully satisfied chemists, and many new formulas for benzene have been proposed since Kekulé's time. A few of these inventions deserve consideration.

A structure proposed by Armstrong and independently by Baeyer is often called the "centric" formula. In this arrangement one valence bond of each carbon atom is extended toward the center of the ring. The fourth valence of each carbon atom belongs as much to one as to any other carbon atom in the ring, the six tetrahedral carbon atoms being arranged in such a way as to throw the fourth, or unoccupied, point of each tetrahedron toward the center of the group.

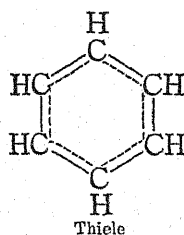
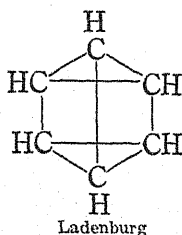
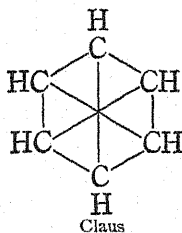


If each carbon atom were independently unsaturated, having one free bond, as indicated in the centric formula, it should be possible to introduce a single halogen or other univalent group, forming a compound of the type  $C_6H_6X$ . This is not the case. Invariably the addition products formed belong to the types  $C_6H_6X_2$ ,  $C_6H_6X_4$ , and  $C_6H_6X_6$ . The centric formula does afford an explanation of the fact that it is much more difficult to bring about the addition of the first pair of elements than it is to introduce the second and third pairs. If the inactivity of the free valences is due to their symmetrical arrangement,

\* For properties that have led some chemists to believe that such isomers exist see Ostromisslensky, *Z. physik. Chem.*, 57, 341 (1906).

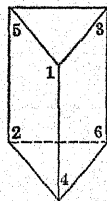
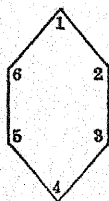
then as soon as two of the bonds have been withdrawn from the central group the symmetry has been destroyed and the remaining bonds are less firmly held in place.

Arguments have been made in support of each of the following structures and there are objections to each :



Thiele's formula is perhaps the best of the group. The dotted lines represent partial valences. They are unreactive, for the formula as a whole is an example of what is known as a conjugated system. The merits and limitations of this structure are discussed under conjugation and resonance.

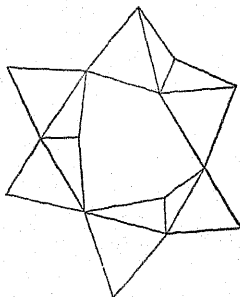
The Ladenburg formula represents the benzene molecule as a triangular prism. This formula provides for the formation of addition products, but only by breaking a single bond between carbon atoms. The number of isomeric forms of polysubstitution products is as well accounted for as by the Kekulé, Baeyer, and Thiele formulas. From the number of trisubstitution products that may be derived from a given disubstitution product it is possible to determine which positions in the Ladenburg formula correspond to the *ortho*, *meta*, and *para* positions of the Kekulé formula. For reference the corresponding positions are numbered in the following diagrams :







It should be possible to secure stereoisomeric disubstitution products of benzene if the hydrocarbon corresponds to the Ladenburg formula, but no such isomerism has been observed.\*

\* For other objections to this structure and for a more complete discussion of all these formulas, see Stewart's "Stereochemistry."

On the basis of the Kekulé formula, the arrangement of the atoms in space is shown in the following diagram:



The centers of the six carbon atoms lie in one plane. No case of optical activity has yet been traced to asymmetry in the benzene nucleus. This, of course, does not exclude from consideration space formulas that present such possibilities; for stereoisomers may exist which we cannot separate or detect by methods now at our command.

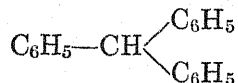
The simple hexagon, , will be used throughout this text as an abbreviation for the structural formula of benzene. The univalent phenyl radical,  $C_6H_5-$ , derived from benzene by loss of one hydrogen atom, will be written  $C_6H_5-$  or represented by the symbol  or by the Greek letter  $\phi$ . Thus, bromobenzene will be written  $C_6H_5Br$ , Br, or  $\phi Br$ ; and benzene itself will be written  $C_6H_6$ , , or  $\phi H$ . Radicals derived from the aromatic hydrocarbons are designated *aryl radicals*.

### HOMOLOGUES OF BENZENE

By direct or indirect means, the hydrogen atoms in benzene may be replaced by alkyl or aryl radicals, and thus various types of hydrocarbons genetically related to benzene may be prepared.

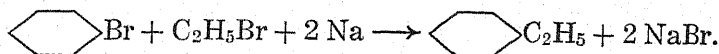
An alkyl radical or other group attached to the benzene ring in the place of hydrogen is referred to as a side chain, and the benzene residue is called the nucleus of the molecule. A side


chain may consist of an aliphatic group, as in toluene,  $\text{C}_6\text{H}_5 \cdot \text{CH}_3$ , or it may be exclusively aromatic in character, as in biphenyl,  $\text{C}_6\text{H}_5 \cdot \text{C}_6\text{H}_5$ , or it may be composed of an aliphatic group in which hydrogen has been replaced by aryl radicals, as in triphenylmethane,



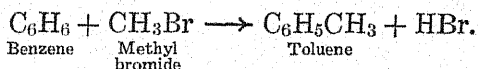
The following general methods are employed in the synthesis of homologues of benzene:

1. **The Fittig synthesis.** A reaction corresponding to the Wurtz synthesis consists of treating a mixture of an aryl halide and an alkyl halide with sodium. Thus bromobenzene and ethyl bromide yield ethylbenzene:



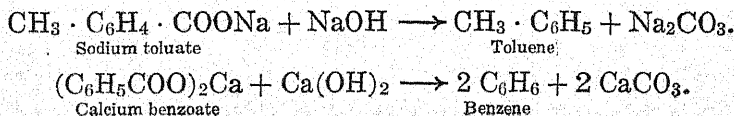
Mixed products are obtained in this reaction, for ethyl radicals unite, forming butane,  $\text{C}_2\text{H}_5 \cdot \text{C}_2\text{H}_5$ , and phenyl radicals combine to form biphenyl, .

2. **The Friedel and Crafts reaction.** Homologues of benzene may be made by the action of an alkyl halide on an aromatic hydrocarbon in the presence of dry aluminum chloride:

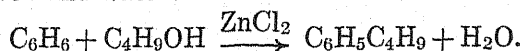


This is an important general reaction. The aluminum chloride is regarded as a catalyst, although in some cases it is necessary to use as many moles of  $\text{AlCl}_3$  as there are moles of the reacting hydrocarbon, and in many cases there is evidence of the formation of an intermediate product containing the aromatic nucleus combined with aluminum and chlorine.

3. **Distillation of a salt.** Dry distillation of a mixture of a base and a salt of an acid results in the destruction of the carboxyl group and the formation of a hydrocarbon:



4. A mixture of an aromatic hydrocarbon and an alcohol, if heated (300°) with zinc chloride in a sealed tube, yields a higher hydrocarbon and water:

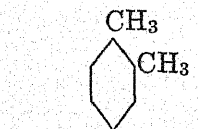


Physical constants of a few of the homologues of benzene are given in the following table:

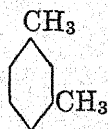
| NAME                         | FORMULA  | MELTING POINT | BOILING POINT | SPECIFIC GRAVITY |
|------------------------------|--|---------------|---------------|------------------|
| Toluene . . . . .            | $\text{C}_6\text{H}_5\text{CH}_3$                          | - 95.1°       | 110.5°        | 0.866 (20°)      |
| Xylene (o) . . . . .         | $\text{C}_6\text{H}_4(\text{CH}_3)_2$                      | - 27.1°       | 144°          | 0.893 (0°)       |
| Xylene (m) . . . . .         | $\text{C}_6\text{H}_4(\text{CH}_3)_2$                      | - 53.6°       | 139°          | 0.881 (0°)       |
| Xylene (p) . . . . .         | $\text{C}_6\text{H}_4(\text{CH}_3)_2$                      | + 13.2°       | 138°          | 0.861 (20°)      |
| Hemimellitene . . . . .      | $\text{C}_6\text{H}_3(\text{CH}_3)_3$ 1, 2, 3              | —             | 176.5°        | 0.895 (20°)      |
| Pseudocumene . . . . .       | $\text{C}_6\text{H}_3(\text{CH}_3)_3$ 1, 2, 4              | - 61°         | 169.8°        | 0.879 (20°)      |
| Mesitylene . . . . .         | $\text{C}_6\text{H}_3(\text{CH}_3)_3$ 1, 3, 5              | - 52.7°       | 164.5°        | 0.869 (10°)      |
| Ethylbenzene . . . . .       | $\text{C}_6\text{H}_5\text{C}_2\text{H}_5$                 | - 92.8°       | 134°          | 0.883 (0°)       |
| Cumene . . . . .             | $\text{C}_6\text{H}_5\text{C}_3\text{H}_7$ (iso)           | —             | 153.4°        | 0.879 (0°)       |
| Propylbenzene . . . . .      | $\text{C}_6\text{H}_5\text{C}_3\text{H}_7$ (n)             | - 101.6°      | 157.5°        | 0.881 (0°)       |
| Cymene . . . . .             | $\text{C}_6\text{H}_4\text{CH}_3\text{C}_3\text{H}_7$ 1, 4 | - 73.5°       | 176°          | 0.872 (0°)       |
| Pentamethylbenzene . . . . . | $\text{C}_6\text{H}(\text{CH}_3)_5$                        | + 53°         | 230°          | 0.847 (107°)     |
| Hexamethylbenzene . . . . .  | $\text{C}_6(\text{CH}_3)_6$                                | 166°          | 265°          | —                |
| Hexaethylbenzene . . . . .   | $\text{C}_6(\text{C}_2\text{H}_5)_6$                       | 129°          | 298°          | 0.831 (130°)     |

*Toluene*,  $\text{C}_6\text{H}_5\text{CH}_3$ , a mobile, colorless liquid, is obtained from coal tar by distillation, or it may be prepared synthetically by some of the methods given above. It is the source of the high explosive trinitrotoluene and of many useful reagents such as benzyl chloride, benzaldehyde, and benzoic acid.

*Xylenes*. The three xylenes occur in coal tar. They are represented by the following formulas:



Orthoxylene  
(m.p. - 27.1°, b.p. 144°)



Metaxylene  
(m.p. - 53.6°, b.p. 139°)



Paraxylene  
(m.p. 13.2°, b.p. 138°)

The *ortho* and *para* xylenes are oxidized by hot dilute nitric acid to the corresponding toluic acids,  $\text{C}_6\text{H}_4 \begin{matrix} \text{CH}_3 \\ \diagup \\ \text{COOH} \end{matrix}$ . The oxidation of *metaxylene* by dilute nitric acid proceeds so slowly that it is possible to separate *metaxylene* from its isomers in

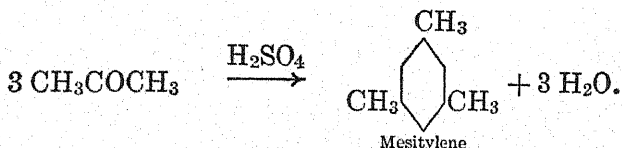
this way. It is not practical to separate them by distillation. The isolation of each of the three xylenes from the mixture obtained from coal tar is accomplished by shaking the mixture with concentrated sulfuric acid. *Ortho* and *meta* xylenes are

converted into xylene sulfonic acids,  $\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{C}_6\text{H}_3\text{SO}_3\text{H}$ , and

*paraxylene* is unchanged. The sodium salts of the *ortho* and *meta* xylene sulfonic acids are separated by fractional crystallization, and the free hydrocarbons are obtained by hydrolyzing the salts with hot hydrochloric acid or by boiling them with a solution of ammonium chloride.

*p-Cymene*,  $\text{CH}_3\text{C}_6\text{H}_4\text{C}_3\text{H}_7$ , is found in lemon oil, eucalyptus oil, and in many other essential oils. It may be made by heating camphor with phosphorus pentoxide.

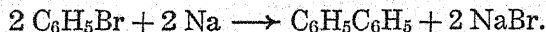
*Mesitylene*,  $(\text{CH}_3)_3\text{C}_6\text{H}_3$ , is prepared by mixing acetone and concentrated sulfuric acid and distilling the mixture several hours later. The reaction consists of a condensation of three molecules of acetone, with loss of water:



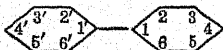
*Diphenyl*,  $\text{C}_6\text{H}_5\text{C}_6\text{H}_5$  (m.p.  $69^\circ$ , b.p.  $254.9^\circ$ ), crystallizes from hot alcohol in large colorless plates. It is formed by passing benzene vapor through a red-hot tube; this is the best laboratory method for making it:\*



Sodium acts on bromobenzene in ether, producing diphenyl:



The positions of the carbon atoms in diphenyl are numbered as follows:

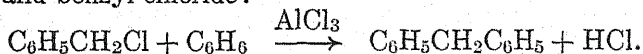


Bromine and chlorine form substitution products with diphenyl, the first halogen atom entering the molecule in position 4 (or 4').

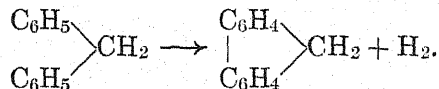
\* Fischer, Anleitung zur Darstellung organischer Präparate.

On further treatment, a 4, 4'-dihalogen substitution product is formed. Nitric acid converts the hydrocarbon into 2-nitrobiphenyl, 4-nitrobiphenyl, 2, 4'-dinitrobiphenyl, and 4, 4'-dinitrobiphenyl. Chromic acid removes one of the rings, as it would an aliphatic side chain, the principal product formed being benzoic acid,  $\text{C}_6\text{H}_5\text{COOH}$ .

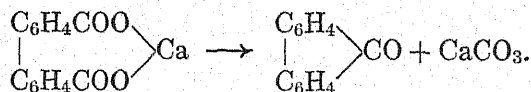
*Diphenylmethane*,  $(\text{C}_6\text{H}_5)_2\text{CH}_2$  (m.p.  $27^\circ$ , b.p.  $262^\circ$ ), is prepared by the action of aluminum chloride on a mixture of benzene and benzyl chloride:



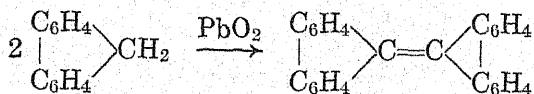
Diphenylmethane is easily oxidized by chromic acid to benzophenone,  $\text{C}_6\text{H}_5\text{COC}_6\text{H}_5$ . At high temperatures the vapor of diphenylmethane is decomposed, yielding fluorene and hydrogen:



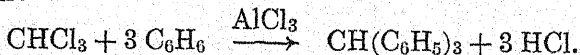
Fluorene melts at  $116^\circ$ , boils at  $295^\circ$ , and forms beautiful fluorescent crystals. On oxidation fluorene yields diphenylene ketone,  $\begin{array}{c} \text{C}_6\text{H}_4 \\ | \\ \text{CO} \\ | \\ \text{C}_6\text{H}_4 \end{array}$ , a compound produced also by distilling the calcium salt of diphenic acid:



Fluorene is oxidized by lead dioxide at  $330^\circ$ , forming a bright red, solid hydrocarbon, dibiphenylene ethylene (m.p.  $188^\circ$ ):



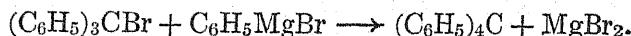
*Triphenylmethane*,  $(\text{C}_6\text{H}_5)_3\text{CH}$  (m.p.  $93^\circ$ , b.p.  $359^\circ$ ), is obtained from chloroform and benzene by Friedel and Crafts' reaction:



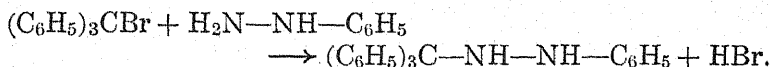
The hydrocarbon is oxidized by lead dioxide or other mild oxidizing agents to triphenyl carbinol,  $(\text{C}_6\text{H}_5)_3\text{COH}$ , a colorless

crystalline body, melting at 162.5°. The hydroxyl of the carbinol is, in turn, easily replaced by chlorine through the agency of acetyl chloride or even by hydrogen chloride, and the chloride reverts spontaneously to the carbinol if exposed to moist air.

*Tetraphenylmethane*,  $(\text{C}_6\text{H}_5)_4\text{C}$  (m.p. 285°, b.p. 431°), a colorless, crystalline hydrocarbon, insoluble in alcohol, ether, and cold acetic acid, but fairly soluble in hot benzene, may be prepared through the action of phenyl magnesium bromide on triphenylmethyl bromide (Grignard reaction):



The yield is only 5 per cent to 10 per cent of the theoretical. Many unsuccessful attempts to prepare this compound were made during the last half of the nineteenth century. The synthesis was finally accomplished by Gomberg\* through the action of phenylhydrazine on triphenylbromomethane:

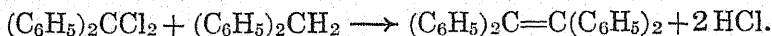


This crystalline product, triphenylmethylhydrazobenzene (m.p. 137°), when dissolved in ether, absorbs oxygen from the air, forming triphenylmethylazobenzene, a crystalline compound melting at 114° and having the formula



The latter decomposes between 120° and 130° into nitrogen and tetraphenylmethane.

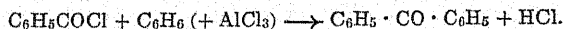
*Tetraphenylethylene* (m.p. 221°, b.p. 425°) is a representative aromatic unsaturated hydrocarbon. It is prepared by heating benzophenone chloride † with diphenylmethane:



Unlike most unsaturated compounds, this hydrocarbon does not form an addition product with bromine nor with halogen acids. Chlorine, however, does react with it by addition.

\* Gomberg, *Ber.*, 30, 2043 (1897).

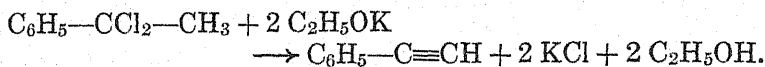
† Benzophenone (m.p. 48.5°, b.p. 305°) is made, by Friedel and Crafts' reaction, from benzoyl chloride and benzene:



Phosphorus pentachloride converts this ketone into benzophenone chloride,  $\text{C}_6\text{H}_5 \cdot \text{CCl}_2 \cdot \text{C}_6\text{H}_5$ .



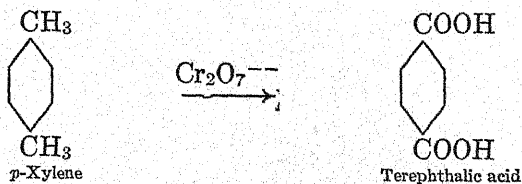
*Phenylacetylene* (b.p.  $143^{\circ}$ ) is made by the removal of hydrogen chloride from acetophenone chloride, through the agency of alcoholic potash:



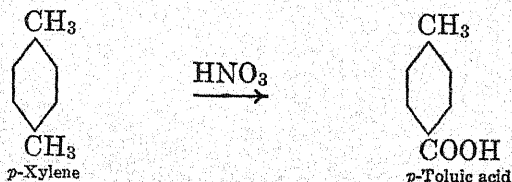
This compound acts like other acetylene derivatives, forming addition products readily, and precipitating compounds of silver and copper from ammoniacal solutions of salts of these metals.

**Oxidation of side chains.** Chromic acid, nitric acid, hot acid or alkaline solutions of permanganates, and some other oxidizing agents convert side chains into carboxyl groups. Regardless of the length or structure of the side chain, it is removed in the form of carbon dioxide and water, or other compounds of low molecular weight, leaving only the carbon atom which is attached directly to the nucleus, this carbon remaining as part of a carboxyl group. Thus, toluene,  $\text{C}_6\text{H}_5 \cdot \text{CH}_3$ , ethylbenzene,  $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{CH}_3$ , and isobutyl benzene,  $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{CH}(\text{CH}_3)_2$ , yield the same compound, benzoic acid,  $\text{C}_6\text{H}_5 \cdot \text{COOH}$ , when oxidized. Oxidation of such compounds by physiological processes often results in the formation of acids in which the carboxyl group is not attached to the ring. Phenylbutyric acid,  $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COOH}$ , is oxidized, in the living cells of the body, to phenylacetic acid,  $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{COOH}$ .

If more than one side chain is attached to the same ring, a polybasic acid is produced. Thus *paraxylene* yields terephthalic acid:



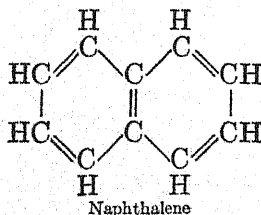
It is possible, however, to oxidize one side chain and leave another intact. Dilute nitric acid converts *paraxylene* into *para*-toluic acid:



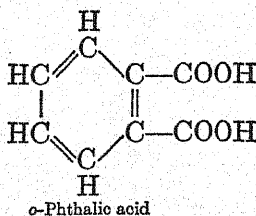
Benzene derivatives containing two side chains in *ortho* positions are oxidized to dibasic acids by permanganate ions, but they are often oxidized to carbon dioxide and water by dichromate ions.

### CONDENSED NUCLEI

*Naphthalene*,  $C_{10}H_8$ , is obtained from coal tar. It crystallizes from hot alcohol or ether in shining, colorless plates, melting at  $80^\circ$  and boiling at  $218^\circ$ . It is insoluble in water, sublimes slowly at room temperature, distills with steam, and has a characteristic odor. It is used in enormous quantities in the manufacture of the azo dyes, in the preparation of moth balls, in illuminating gas to increase the luminosity of the flame, and in the manufacture of phthalic acid. The naphthalene molecule consists of two benzene nuclei, having two carbon atoms in common:

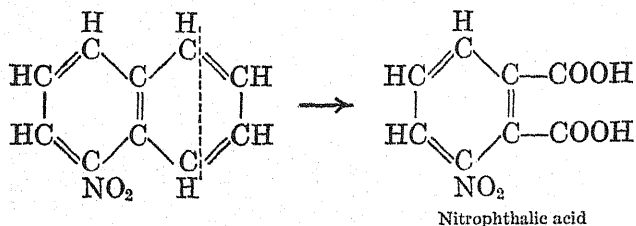


When oxidized, naphthalene yields *orthophthalic acid*:

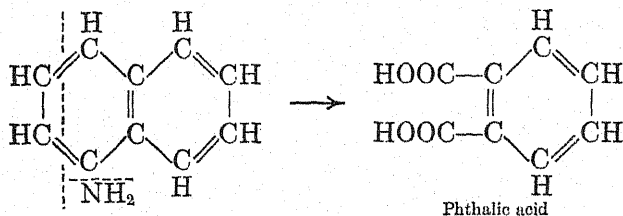


This indicates that naphthalene contains a benzene ring with two side chains in *ortho* positions. That the two side chains constitute another benzene ring is shown as follows. Nitro substitution products of benzene are less susceptible to oxidation than are unsubstituted rings. Amino derivatives of benzene are more easily oxidized than are the unsubsti-

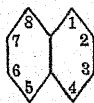
tuted rings. Now, nitronaphthalene on oxidation yields nitrophthalic acid:



If the nitro group be reduced to an amino group before the oxidation is effected, then the substituted ring is broken, and ordinary unsubstituted phthalic acid is formed:



Naphthalene yields two isomeric monosubstitution products; ten disubstitution products if the substituents are alike, and fourteen if the two entering elements or groups are unlike. The positions in the molecule where substitution may occur are numbered as follows:

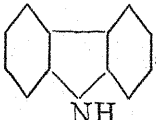


It is obvious that a group attached to carbon atom 1, 4, 5, or 8 makes a compound that is not identical with the substance formed by placing the same substituent in position 2, 3, 6, or 7. The first numbers (1, 4, 5, and 8) are called *alpha* positions, the others are *beta* positions. Disubstitution products are often designated as *ortho*, *meta*, and *para* when the substituents are in the same ring, but numbers or letters are used when positions in both rings must be indicated.

At temperatures between 700° and 1000° naphthalene and other aromatic hydrocarbons are formed in small quantities

from propane, butane, and other paraffins containing fewer than six carbon atoms, as well as from the higher members of the methane series.\*

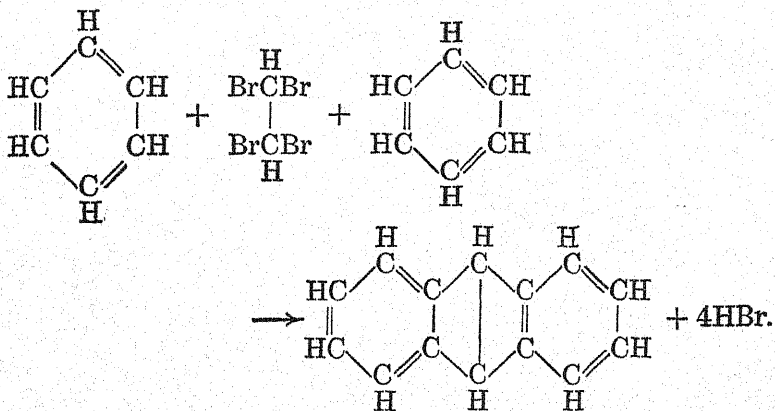
*Anthracene*,  $C_{14}H_{10}$  (m.p.  $218^\circ$ , b.p.  $342^\circ$ ), is obtained from coal tar, in which it occurs to the extent of 0.3 per cent to 0.5 per cent. Phenanthrene and carbazole are found in the same fraction and are not separated from anthracene by distillation

alone. Carbazole, , is removed by distilling the

mixture with potassium carbonate. The nonvolatile potassium carbazole,  $\begin{array}{c} C_6H_4 \\ | \\ C_6H_4 \end{array} \rangle NK$ , remains in the retort. Phenanthrene is removed by extraction with carbon disulfide, in which it is very soluble.

When it is exposed to light, anthracene polymerizes to di-anthracene,  $C_{28}H_{20}$ . In the dark this polymer reverts to anthracene. Many other reversible photochemical reactions are known.

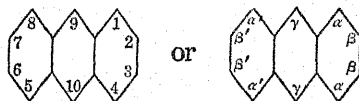
Anthracene may be prepared, by Friedel and Crafts' reaction, from tetrabromoethane and benzene:



Other methods of preparation and most of the properties of anthracene indicate that the molecule has this structure.

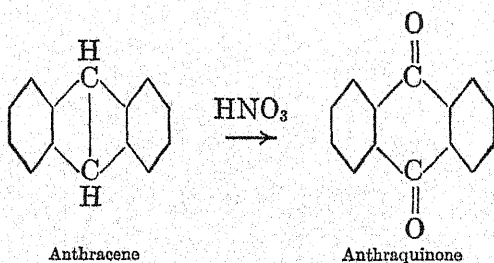
\* Zanetti, *J. Ind. and Eng. Chem.*, 8, 674 (1916).

Positions in the molecule are indicated by numbers or by letters:



Three monosubstitution products of anthracene may exist, and in many cases the three have been prepared. Fifteen disubstitution products could be made with similar substituents and many more with unlike groups. Not all these possibilities have been realized.

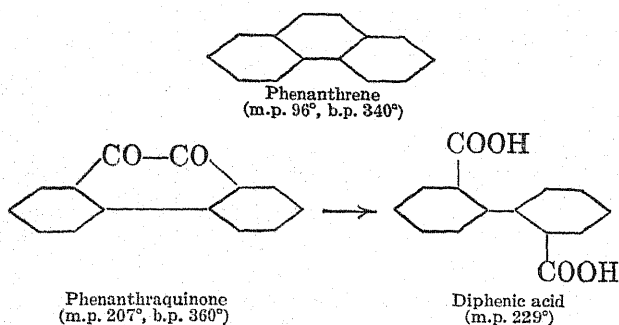
Anthracene crystallizes in shining, fluorescent leaflets. It is insoluble in water, sparingly soluble in alcohol and ether, but it dissolves readily in hot benzene. It forms an insoluble compound with picric acid,  $C_{14}H_{10} \cdot C_6H_2(NO_2)_3OH$ . This product crystallizes in red needles that melt at  $138^\circ$ . A method for the quantitative estimation of anthracene is based on this reaction. Positions 9 and 10 are very reactive. Sodium amalgam in alcohol causes addition of hydrogen to each of these carbon atoms. Bromine rapidly replaces hydrogen in positions 9 and 10. A satisfactory laboratory method for making hydrobromic acid consists in dropping bromine on anthracene. Nitric acid oxidizes anthracene in positions 9 and 10, forming anthraquinone. The reaction proceeds so rapidly that it is not possible to secure a nitro derivative of the unoxidized hydrocarbon:



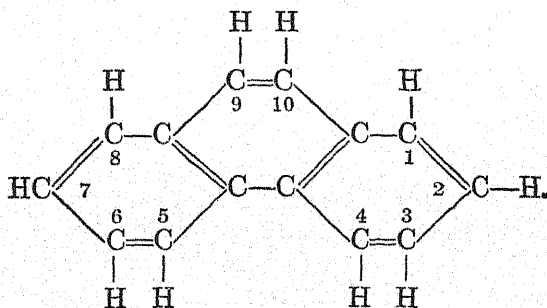
Further treatment with nitric acid yields nitro derivatives of anthraquinone.

*Phenanthrene*,  $C_{14}H_{10}$ , a coal-tar product isomeric with anthracene, crystallizes in colorless plates. It dissolves in alcohol, forming a blue fluorescent solution. A mixture of sulfuric acid

and potassium dichromate converts it first into phenanthraquinone and ultimately into diphenic acid :

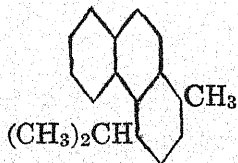


The carbon atoms that are attached to hydrogen in the phenanthrene molecule are numbered as follows :



Anthracene is a valuable source of alizarin dyes and intermediates, but no important uses have been found for its isomer, phenanthrene.

*Reten*,  $C_{18}H_{18}$ , a homologue of phenanthrene, occurs in the gum and pitch of spruce and pine trees. It is 1-methyl-4-isopropylphenanthrene,



It crystallizes in large leaflets with pearly luster, melts at 98.5°, and boils at 394°. It forms a molecular compound with picric acid that crystallizes in yellow needles, melting at 124°.

# HYDROCARBON DERIVATIVES

## ARYL HALIDES

When benzene is floated on a solution of dilute sodium hydroxide and chlorine gas is bubbled through the mixture, an addition product,  $C_6H_6Cl_6$ , is formed. When chlorine is passed into benzene in the presence of certain catalysts (halogen carriers), substitution of the halogen for hydrogen occurs, with the formation of compounds of the types  $C_6H_5Cl$ ,  $C_6H_4Cl_2$ , and so on to  $C_6Cl_6$ . The most effective catalysts are aluminum chloride, iron filings, tin, iodine, and zinc chloride. Aromatic hydrocarbons having aliphatic side chains may be chlorinated either in the ring or in the side chain, the course of the reaction being determined by the control of the experimental conditions. In the absence of direct sunlight and in the presence of a catalyst, substitution occurs in the ring. In sunlight or at high temperatures, in the absence of a catalyst, substitution occurs in the side chain. The substitution of bromine for hydrogen in the nucleus or in the side chain of an aromatic hydrocarbon is accomplished in the same way. The iodides are prepared by indirect methods.

Physical constants of a few halogen derivatives of aromatic hydrocarbons are given in the following tables:

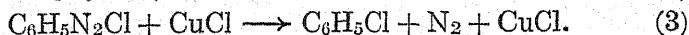
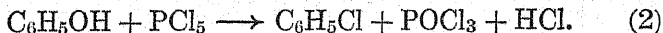
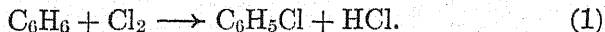
### CHLORINE COMPOUNDS

| NAME                                 | FORMULA        | MELTING POINT | BOILING POINT | SPECIFIC GRAVITY |
|--------------------------------------|----------------|---------------|---------------|------------------|
| Chlorobenzene . . . . .              | $C_6H_5Cl$     | - 45.2°       | 132°          | 1.106 (20°)      |
| 1, 2-Dichlorobenzene . . . .         | $C_6H_4Cl_2$   | - 17.6°       | 179°          | 1.325 (0°)       |
| 1, 3-Dichlorobenzene . . . .         | $C_6H_4Cl_2$   | - 24.8°       | 173°          | 1.307 (0°)       |
| 1, 4-Dichlorobenzene . . . .         | $C_6H_4Cl_2$   | + 52°         | 173°          | 1.241 (63°)      |
| 1, 2, 4-Trichlorobenzene . .         | $C_6H_3Cl_3$   | + 17°         | 213°          | 1.446 (26°)      |
| <i>Ortho</i> chlorotoluene . . . . . | $C_6H_4ClCH_3$ | - 35.1°       | 159.4°        | 1.085 (18°)      |
| <i>Meta</i> chlorotoluene . . . . .  | $C_6H_4ClCH_3$ | - 47.8°       | 162.4°        | 1.072 (20°)      |
| <i>Para</i> chlorotoluene . . . . .  | $C_6H_4ClCH_3$ | + 7.8°        | 162.5°        | 1.071 (18°)      |
| Benzyl chloride . . . . .            | $C_6H_5CH_2Cl$ | - 39°         | 179.4°        | 1.103 (18°)      |
| Benzal chloride . . . . .            | $C_6H_5CHCl_2$ | - 17.4°       | 214°          | 1.295 (16°)      |
| Benzotrichloride . . . . .           | $C_6H_5CCl_3$  | - 4.8°        | 220.7°        | 1.378 (15°)      |

## BROMINE COMPOUNDS

| NAME                        | FORMULA                                | MELTING POINT | BOILING POINT | SPECIFIC GRAVITY     |
|-----------------------------|--|---------------|---------------|----------------------|
| Bromobenzene . . . . .      | $C_6H_5Br$                             | $-30.5^\circ$ | $156.2^\circ$ | 1.497 ( $20^\circ$ ) |
| 1, 2-Dibromobenzene . . .   | $C_6H_4Br_2$                           | $+1.8^\circ$  | $221^\circ$   | 2.003 ( $0^\circ$ )  |
| 1, 3-Dibromobenzene . . .   | $C_6H_4Br_2$                           | $-6.9^\circ$  | $217^\circ$   | 1.955 ( $20^\circ$ ) |
| 1, 4-Dibromobenzene . . .   | $C_6H_4Br_2$                           | $+86.8^\circ$ | $219^\circ$   | 1.954 ( $20^\circ$ ) |
| 1, 2, 3-Tribromobenzene . . | $C_6H_3Br_3$                           | $87.4^\circ$  | —             | 2.658 ( $20^\circ$ ) |
| 1, 2, 4-Tribromobenzene . . | $C_6H_3Br_3$                           | $44^\circ$    | $276^\circ$   | —                    |
| 1, 3, 5-Tribromobenzene . . | $C_6H_3Br_3$                           | $120^\circ$   | $278^\circ$   | —                    |
| Orthobromotoluene . . . .   | $C_6H_4BrCH_3$                         | $-28.1^\circ$ | $181.8^\circ$ | 1.422 ( $20^\circ$ ) |
| Metabromotoluene . . . .    | $C_6H_4BrCH_3$                         | $-39.8^\circ$ | $183.7^\circ$ | 1.410 ( $20^\circ$ ) |
| Parabromotoluene . . . .    | $C_6H_4BrCH_3$                         | $+28.2^\circ$ | $183.6^\circ$ | 1.310 ( $20^\circ$ ) |
| Benzyl bromide . . . . .    | $C_6H_5CH_2Br$                         | $-3.9^\circ$  | $199^\circ$   | 1.438 ( $22^\circ$ ) |
| Orthoxylyl bromide . . . .  | $C_6H_4CH_3CH_2Br$                     | $+21^\circ$   | $217.7^\circ$ | 1.380 ( $22^\circ$ ) |
| Dibromo-metaxylene . . .    | $C_6H_2Br_2(CH_3)_2$<br>(4, 6—1, 3)    | $72^\circ$    | $256^\circ$   | —                    |
| Tribromomesitylene . . .    | $C_6Br_3(CH_3)_3$<br>(2, 4, 6—1, 3, 5) | $224^\circ$   | —             | —                    |

*Chlorobenzene.* Phenyl chloride,  $C_6H_5Cl$ , a colorless liquid having an agreeable odor, boils at  $132^\circ$  and melts at  $-45.2^\circ$ . It is insoluble in water, but dissolves in all proportions in alcohol and in ether. It is prepared (1) by direct chlorination of benzene, or (2) by the action of phosphorus pentachloride on phenol, or (3) by warming benzene diazonium chloride with cuprous chloride:



The second equation represents a method that is not very useful. The hydroxyl group in a phenol is not easily replaced, even under the influence of a powerful reagent like phosphorus pentachloride, and the yield of the halogen derivative is always small. In this respect phenols differ from alcohols.

*Bromobenzene.* Phenyl bromide,  $C_6H_5Br$ , resembles chlorobenzene in most respects and is prepared by similar methods. It melts at  $-30.5^\circ$ , boils at  $156.2^\circ$ , and has a specific gravity of 1.497 at  $20^\circ$ .

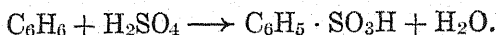
*Iodobenzene.* Phenyl iodide,  $C_6H_5I$ , is a colorless liquid having a density of 1.861 at  $0^\circ C$ . It melts at  $-31.4^\circ$  and boils at  $188.6^\circ$ . It is usually prepared by means of the diazo reaction (see pages 224 and 227). Iodine does not act upon



benzene at low temperatures, but the preparation of  $\text{C}_6\text{H}_5\text{I}$  can be accomplished by heating a mixture of benzene, iodine, and iodic acid in a sealed tube. The hydrogen iodide formed is oxidized to iodine and water by the iodic acid, and reversal of the process of substitution is thus prevented.

### SULFONIC ACIDS

Fuming sulfuric acid acts upon aromatic hydrocarbons forming sulfonic acids. Ordinary concentrated sulfuric acid accomplishes the same thing but requires a higher temperature and a longer time:



If fuming sulfuric acid is used, two or even three hydrogen atoms may be replaced by  $\text{SO}_3\text{H}$  groups. The formation of benzenetrisulfonic acid is catalyzed by silver sulfate.

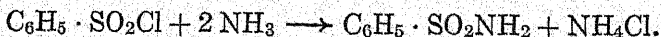
The sulfur atom in a sulfonic acid is linked to carbon directly and not through oxygen, as indicated by the fact that thiophenol,  $\text{C}_6\text{H}_5\text{SH}$ , when oxidized, yields the same benzenesulfonic acid that is produced by the action of sulfuric acid on benzene.

The free aromatic sulfonic acids are colorless, crystalline compounds. They are soluble in water and most of their metallic derivatives are soluble. The separation of benzenesulfonic acid from the excess of sulfuric acid used in the reaction is accomplished by diluting the mixture and neutralizing it with barium carbonate. The barium salt of the sulfonic acid is soluble. It is freed from the precipitated barium sulfate by filtration and obtained in crystalline form by evaporation of the filtrate. The free acid is obtained from the salt by treatment with the calculated quantity of sulfuric acid.

The free acid or the salt may be converted into an acid chloride by treatment with phosphorus pentachloride:

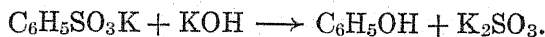


Benzenesulfonyl chloride,  $\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$ , is an oily liquid (sp. gr. 1.384, m.p.  $14.5^\circ$ , b.p.  $247^\circ$ ). Corresponding derivatives of the homologues of benzene are solids at room temperature. From them the sulfonic amides are prepared by the action of ammonia or ammonium carbonate:



Reactions of benzenesulfonyl chloride with primary and secondary amines have been mentioned (see page 139).

Groups that cannot be substituted for hydrogen directly may often be introduced into the ring through the agency of sulfonic acids. This is, in fact, one of the most important applications of sulfonation in the aromatic series. The hydroxyl group is introduced by fusing the potassium salt of a sulfonic acid with potassium hydroxide. Many phenols and naphthols are prepared commercially by means of this reaction:

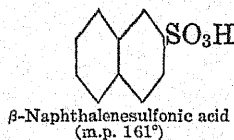
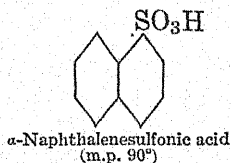


Nitriles are formed by fusing the salt of a sulfonic acid with potassium cyanide:



Sodium amide serves to introduce the amino group, and in many cases concentrated nitric acid substitutes the nitro group for the  $\text{SO}_3\text{H}$  radical.

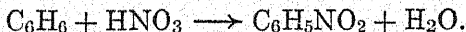
Naphthalenesulfonic acids are formed by the direct action of sulfuric acid upon naphthalene. When the reaction occurs at temperatures below  $100^\circ$ ,  $\alpha$ -naphthalenesulfonic acid is the principal product. Higher temperatures promote the production of the  $\beta$  derivative.



They are colorless, crystalline, deliquescent compounds.

## NITRO COMPOUNDS

Direct nitration of an aromatic compound is accomplished by the action of concentrated nitric acid or a mixture of nitric and sulfuric acids:



Dilution with water promotes ionization of the nitric acid and retards the change. Hydroxyl groups and not hydrogen ions must be furnished by the nitric acid. By using a large excess of sulfuric acid to absorb the water formed in the reac-

tion, the quantity of nitric acid may be reduced to the theoretical requirement as calculated from the equation. This is a matter of economic importance since nitric acid is much more expensive than sulfuric acid.

Nitration is effected at temperatures as low as possible, for nitric acid is a vigorous oxidizing agent and may decompose the compound under treatment. The oxidizing action is accelerated by elevating the temperature. At temperatures below zero it is possible to nitrate some aromatic aldehydes without converting the aldehyde group into a carboxyl group. Aliphatic hydrocarbons require high temperatures for nitration, and in such cases oxidation is checked by using dilute acid. Many derivatives of benzene require a high temperature and high concentration of acid to accomplish nitration, and under these conditions there is usually considerable loss of material through oxidation.

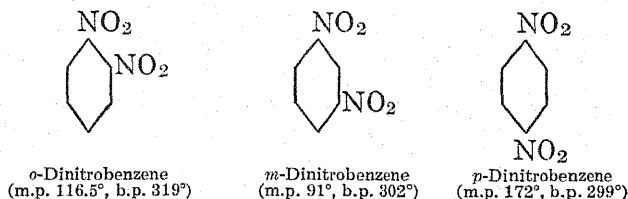
Groups already in the ring influence the rate of nitration. Groups that orient the entering substituent to the *meta* position retard nitration, and groups that orient to the *ortho* and *para* positions facilitate the reaction (see Crum-Brown and Gibson Rule). Benzoic acid,  $C_6H_5COOH$ , resists nitration; but, on the other hand, phenol,  $C_6H_5OH$ , can be nitrated by cold dilute nitric acid. In the case of benzene itself one nitro group is easily introduced, even in the presence of a small amount of water. To place a second nitro group in the same ring one must use concentrated acid. A third nitro group enters only at higher temperatures, and not more than three such groups may be introduced by direct nitration.

Homologues of benzene, having aliphatic side chains, are nitrated in the ring by cold concentrated nitric acid, or in the side chain by hot dilute acid.

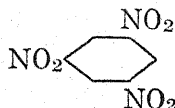
*Nitrobenzene*,  $C_6H_5NO_2$ , is a pale yellow liquid (m.p.  $5.7^\circ$ , b.p.  $210.9^\circ$ , sp. gr. 1.204). It is practically insoluble in water, but it dissolves in alcohol. Its odor resembles that of almonds. It is the chief commercial source of aniline, and is manufactured in large quantities for the production of aniline dyes.

Equal volumes of concentrated nitric acid and concentrated sulfuric acid are mixed and cooled to  $50^\circ$ . The acids are added very slowly and with constant agitation to the benzene. The mixture is stirred and maintained at  $50^\circ$  for about an hour, then poured into a large volume of cold water. Nitrobenzene forms a liquid layer under the water. After washing it free from acid and drying it with calcium chloride, it is distilled.

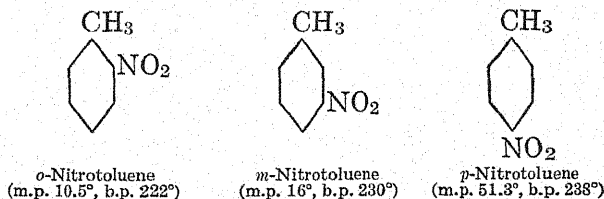
*Dinitrobenzene.* In the ordinary process of making mononitrobenzene, a small quantity of dinitrobenzene appears as a by-product. To make dinitrobenzene the principal product, it is necessary to nitrate at a higher temperature or to employ fuming nitric acid. Three compounds corresponding to the formula  $C_6H_4(NO_2)_2$  are known; but if prepared by direct nitration of benzene, the *meta* compound constitutes by far the greater part of the yield:



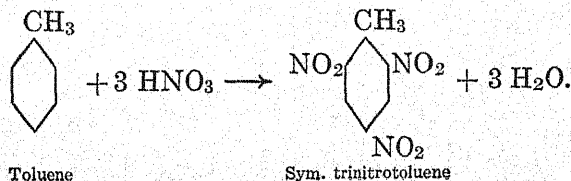
A mixture of concentrated nitric and fuming sulfuric acids converts *metadinitrobenzene* into symmetrical trinitrobenzene,



*Nitrotoluenes.* The first products obtained in the nitration of toluene are *paranitrotoluene* and *orthonitrotoluene*. A very small amount of the *meta* compound is generally formed also:

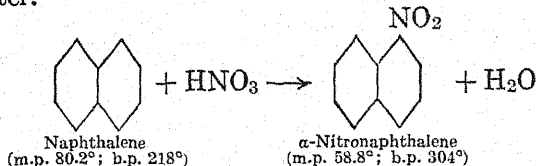


Further nitration produces dinitro bodies and finally one or more of the six isomeric trinitrotoluenes. Symmetrical trinitrotoluene, a powerful explosive, predominates in the mixture:



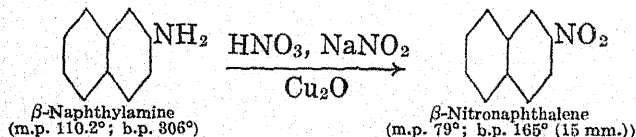
Trinitrotoluene was manufactured in enormous quantities for use in the war of 1914-1918. It was commonly called T.N.T. The substance is a fairly stable pale yellow solid. It can be handled safely, for it is not detonated by an ordinary shock.

*Nitronaphthalenes.* Concentrated nitric acid acts upon naphthalene at room temperature, producing  $\alpha$ -nitronaphthalene, a yellow crystalline compound which is almost insoluble in water.



At higher temperatures the product obtained is a mixture of *mono*-, *di*-, *tri*-, and *tetra*-nitronaphthalenes.

$\beta$ -Nitronaphthalene is obtained from  $\beta$ -naphthylamine through the action of nitric acid and sodium nitrite under catalytic influence of cuprous oxide.\* The nature of this reac-



tion is discussed on page 229.  $\beta$ -Nitronaphthalene crystallizes in the form of rhombic needles. It has a yellow color, dissolves in alcohol or ether, and is practically insoluble in water.

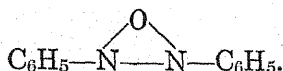
### REDUCTION OF NITROBENZENE

*Nitrosobenzene*,  $\text{C}_6\text{H}_5\text{NO}$ , exists at low temperatures in the form of large colorless monoclinic crystals melting to an emerald green liquid at  $68^\circ$ . It is the first reduction product of nitrobenzene, but cannot be isolated from a reducing medium, since it is rapidly converted to  $\beta$ -phenylhydroxylamine,  $\text{C}_6\text{H}_5\text{NHOH}$ . The reaction is, therefore, allowed to proceed to the  $\beta$ -phenylhydroxylamine stage, and this compound is then oxidized to nitrosobenzene by means of cold chromic acid. Nitrosobenzene explodes when heated with oxygen under

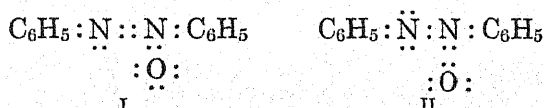
\* For details see Meisenheimer and Witte, *Ber.*, **36**, 4153 (1903).

twenty-five atmospheres of pressure. It combines with aniline, forming azobenzene,  $\text{C}_6\text{H}_5\text{—N=N—C}_6\text{H}_5$ ; with phenylhydroxylamine, forming azoxybenzene,  $(\text{C}_6\text{H}_5)_2\text{N}_2\text{O}$ ; and with hydroxylamine, forming diazobenzene,  $\text{C}_6\text{H}_5\text{—N=N—OH}$ .

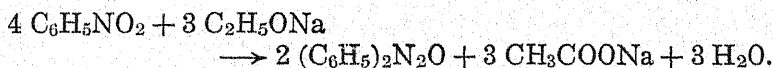
*Azoxybenzene* crystallizes from alcohol in the form of yellow needles, melting at  $36^\circ$ . The compound was formerly represented by the following structure:



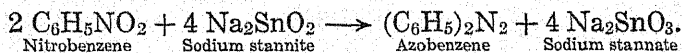
It is now regarded as a resonating molecule in which the following formulas represent limiting positions of the valence electrons. Several other arrangements are possible. It is probable that the vast majority of the molecules in any sample of azoxybenzene correspond to an electron distribution intermediate between these structures, but more closely resembling formula I than formula II:



Azoxybenzene is obtained by reducing nitrobenzene with a hot alcoholic solution of sodium ethylate:



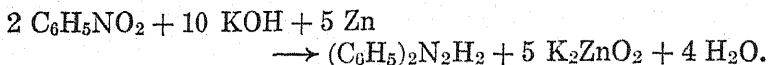
*Azobenzene*,  $\text{C}_6\text{H}_5\text{—N=N—C}_6\text{H}_5$  (m.p.  $67^\circ$ , b.p.  $297.4^\circ$ ), is prepared by reducing nitrobenzene with sodium stannite ( $\text{SnCl}_2$  in an excess of  $\text{NaOH}$ ) or by distilling azoxybenzene with iron filings.



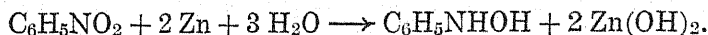
Azobenzene crystallizes in orange-red leaflets. It is insoluble in water but soluble in alcohol and in ether. The compound melts at  $68^\circ$  and boils without decomposition at  $295^\circ$ . It is reduced to hydrazobenzene by treatment with tin and hydrochloric acid.

*Hydrazobenzene*,  $\text{C}_6\text{H}_5\text{—NH—NH—C}_6\text{H}_5$  (m.p.  $131^\circ$ ), is a colorless crystalline compound which decomposes below its boiling point and is converted by mild oxidizing agents, such as ferric chloride or even atmospheric oxygen, to azobenzene.

In the presence of a strong acid it undergoes the Hofmann rearrangement, yielding benzidine. Hydrazobenzene is obtained by reducing an alcoholic solution of nitrobenzene with zinc dust and potassium hydroxide:



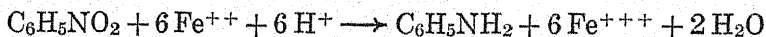
*β-Phenylhydroxylamine*,  $\text{C}_6\text{H}_5\text{NHOH}$ , a colorless, crystalline substance melting at  $82^\circ$ , is obtained from nitrobenzene by the action of zinc dust and hot water or by the electrolytic reduction of nitrobenzene:



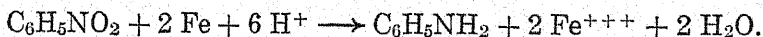
*Aniline*,  $\text{C}_6\text{H}_5\text{NH}_2$ , is the final reduction product of nitrobenzene. It is a compound of very great importance on account of its useful derivatives. It is described in connection with the aromatic amines and the dyes. Aniline is a colorless liquid. It is prepared commercially by warming a mixture of nitrobenzene, iron, and dilute hydrochloric acid:



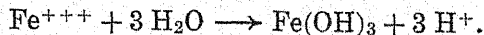
The reaction does not stop with the oxidation of the iron to the ferrous state. Ferrous ions are capable of reducing nitrobenzene:



or

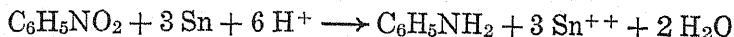


When the added acid has been used in these reactions, the hydrolysis of ferric ions maintains a sufficient hydrogen ion concentration to continue the reduction process as long as free iron and nitrobenzene are present:

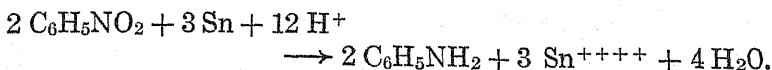


The reduction of nitrobenzene could, therefore, be accomplished by heating it with water, iron, and a ferric salt without the addition of an acid. In the reduction of nitrobenzene with tin and hydrochloric acid, stannic chloride is formed unless an

excess of the metal is used. The reactions leading to the formation of stannous and stannic salts may be written



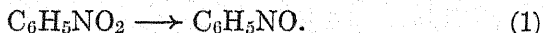
and



Stannic salts, like ferric salts, are readily hydrolyzed. The main stages in the reduction of nitrobenzene by electrolytic processes, whether in acid or in alkaline solution, are: nitrobenzene  $\longrightarrow$  nitrosobenzene  $\longrightarrow$  phenylhydroxylamine  $\longrightarrow$  aniline.

In any reduction process nitro compounds yield mixed products; but, by proper control of the conditions, it is possible to make any required type of product predominate. The ultimate reduction product of a nitro compound is an amine, and if a vigorous reducing agent is employed, this is obtained whether the reaction is carried out in acid, neutral, or alkaline solution. The intermediate products, however, are different in the three cases. By suitable choice of reducing agent and careful control of the hydrogen or hydroxide ion concentration the various intermediate products may be isolated.

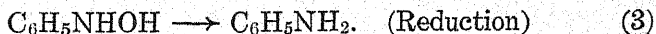
In the first stage, nitrobenzene is converted into nitrosobenzene:



Nitrosobenzene is reduced much more rapidly than is nitrobenzene and therefore it can never accumulate in the reaction mixture. Its transitory existence is proved by the fact that when nitrobenzene is reduced in the presence of hydroxylamine, benzenediazonium hydroxide is formed. This must be accomplished by a reaction between nitrosobenzene and hydroxylamine:

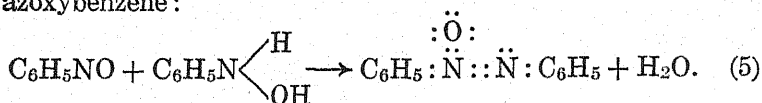


$\beta$ -Phenylhydroxylamine may be isolated if the reduction of nitrobenzene is carried out in neutral solution. In the presence of acids  $\beta$ -phenylhydroxylamine is reduced to aniline or converted by an intramolecular rearrangement into *para*-aminophenol:

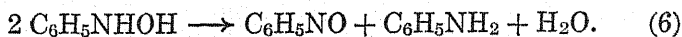




In alkaline solution it condenses with nitrosobenzene, forming azoxybenzene:



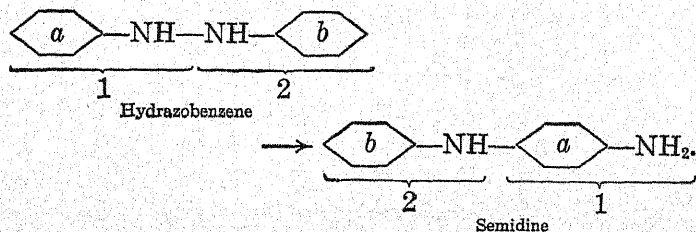
It also undergoes intramolecular oxidation and reduction:



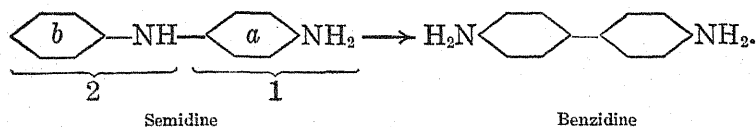
Azoxybenzene, therefore, represents the first product that is obtained from nitrobenzene by reduction in an alkaline medium. Unless a reagent is chosen which carries the reduction to this stage only, the azoxybenzene is converted progressively into azobenzene,  $\text{C}_6\text{H}_5\text{—N=N—C}_6\text{H}_5$ , hydrazobenzene,  $\text{C}_6\text{H}_5\text{—NH—NH—C}_6\text{H}_5$ , and finally to aniline,  $\text{C}_6\text{H}_5\text{NH}_2$ .

Of the compounds listed above, those which contain two nitrogen atoms in the molecule are derived from azoxybenzene. Their production depends upon the condensation between nitrosobenzene and phenylhydroxylamine (equation 5). This proceeds very slowly in the presence of hydrogen ions and rapidly in the presence of hydroxide ions. Hence the azoxy, azo, and hydrazo compounds are not formed in acid reduction but are found among the alkaline reduction products. Unless a proper choice of reducing agent has been made, hydrazobenzene does not accumulate in the reaction mixture; for, in acid solution, it either responds to the benzidine change or is reduced to aniline; and in alkaline solution, it is reduced to aniline, or, if the reducing agent is no longer active, it is oxidized by unchanged nitrobenzene to azoxybenzene and azobenzene.

The benzidine change, which is induced by the presence of hydrogen ions, is an example of the Hofmann rearrangement. The group marked "2" migrates from the nitrogen of group 1 to the *para* position of ring *a*, and the *para* hydrogen of ring *a* passes to the nitrogen of group 1, forming a semidine:



This semidine is still a substituted aniline, and group 1 migrates from the nitrogen of group 2 to the *para* position in ring *b*, the *para* hydrogen of ring *b* passing to the nitrogen of group 2. The final product of this reaction is benzidine:



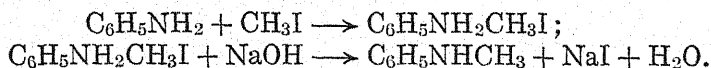
Benzidine crystallizes in colorless, lustrous scales. It melts at 128.7° and boils at 401.7°. Only 0.94 g. of benzidine will dissolve in 100 g. of boiling water, but it is quite soluble in alcohol. Benzidine is manufactured in large quantities for the dye industry.

## AROMATIC AMINES

The aromatic amines are derivatives of ammonia in which hydrogen has been replaced by aryl groups. They are colorless liquids or colorless, crystalline solids, possessing characteristic odors. The primary amines are weak bases. Secondary amines are still weaker, forming salts with strong acids only, and these salts are almost completely hydrolyzed in aqueous solution. Tertiary aromatic amines do not form salts with acids.

Primary aromatic amines are made by reducing the corresponding nitro-compounds. Iron and hydrochloric acid are the reagents commonly used in this reduction process, but many other reagents serve the same purpose. (See reduction of nitrobenzene, page 210.)

Secondary amines are derived from primary amines through several types of reactions. Alkyl halides, for example, form addition products with primary aromatic amines, and subsequent elimination of a halogen acid from the addition product by treatment with an alkali gives rise to mixed aromatic-aliphatic secondary amines:

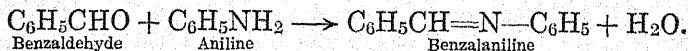


For the preparation of a secondary amine in which both radicals are phenyl groups see page 221.

Tertiary amines are made from secondary amines. Equations representing some of the possible processes are shown in connection with the discussions of triphenylamine and dimethylaniline (pages 222 and 223).

## PRIMARY AMINES

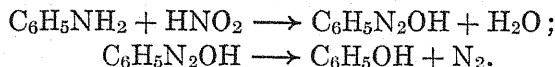
Primary aromatic amines react with aldehydes, eliminating water:



They react with the alkali metals, forming saltlike derivatives in which the metal is attached to nitrogen. Potassium,

for instance, dissolves rapidly in hot aniline, liberating hydrogen and producing the salts  $C_6H_5NHK$  and  $C_6H_5NK_2$ .

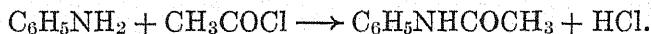
At low temperatures ( $0^\circ$  to  $10^\circ$ ) nitrous acid converts primary aromatic amines into diazonium compounds. At higher temperatures the diazonium salts decompose, with an evolution of nitrogen, yielding phenols. The net result at high temperatures is comparable, therefore, to the production of an alcohol from an aliphatic amine:



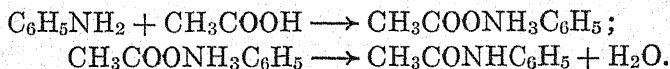
*Aniline* is a colorless liquid, boiling at  $184.4^\circ$ . It is readily nitrated and sulfonated by concentrated nitric acid and sulfuric acid respectively. Water saturated with the amine at ordinary temperatures contains about 3 per cent of aniline by weight. Salts of aniline, such as the hydrochloride,  $C_6H_5NH_2 \cdot HCl$ , and sulfate,  $(C_6H_5NH_2)_2H_2SO_4$ , are crystalline compounds readily soluble in water.

With formaldehyde aniline forms a crystalline condensation product, anhydroformaldehyde aniline,  $(C_6H_5 \cdot N : CH_2)_3$ , melting at  $40^\circ$ . This may be reduced to methylaniline by treatment with tin and hydrochloric acid.

Aniline reacts with acetyl chloride, yielding acetanilide:



Acetanilide is a colorless crystalline compound (m.p.  $114.2^\circ$ , b.p.  $303.8^\circ$ ). It is used in medicine as a febrifuge. The same product may be obtained by heating aniline with acetic acid. Aniline acetate is first formed, but the salt decomposes at  $150^\circ$ , yielding acetanilide and water:

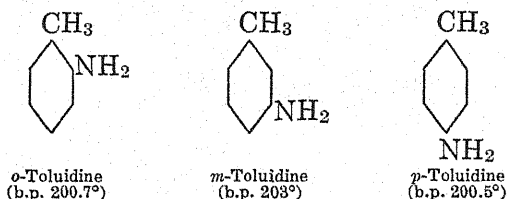


In a solution of bleaching powder aniline produces a violet color. The reaction mixture contains phenylchloroamine,  $C_6H_5NHCl$ , and the color is probably due to a condensation product of phenylchloroamine with aniline.

Aniline is manufactured in large quantities to supply the demands of dye factories. It is used also as a laboratory source of phenols, sulfonic acids, nitroanilines, and homologues of aniline. The preparation of aniline has been described.

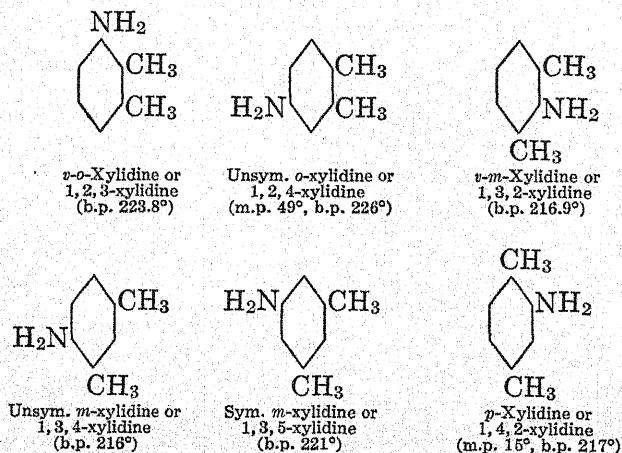
## HOMOLOGUES OF ANILINE

Among the more important compounds derived from aniline by substituting alkyl radicals for hydrogen in the ring are the toluidines and xylidines. There are three toluidines and six xylidines. The toluidines and xylidines resemble aniline in chemical properties, and some of them are used extensively in the dye industry.

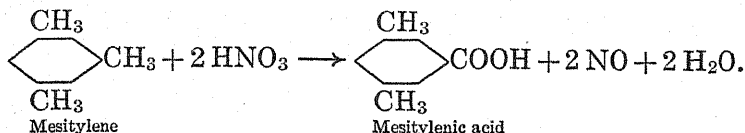


*Orthotoluidine* and *paratoluidine* are prepared by reduction of the corresponding nitro compounds, obtained through direct nitration of toluene. *Orthotoluidine* is a liquid, colorless when pure, but red as ordinarily prepared. *Paratoluidine* is a crystalline solid (m.p. 43.7°). *Metatoluidine*, a liquid, is prepared by reduction of *metanitrobenzal chloride*.

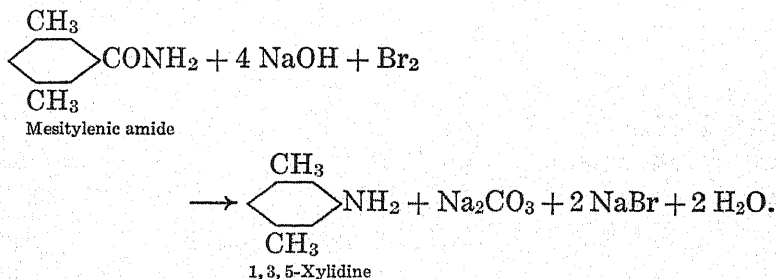
The xylidines are represented by the formulas below. The abbreviations *o*, *m*, *p*, and *v* refer to *ortho*, *meta*, *para*, and *vicinal* positions. A vicinal compound is one having a substituent on each of three adjacent carbon atoms in the nucleus.



Symmetrical *metaxylydine* is prepared from mesitylene. The principal reactions are outlined below.



Nitro compounds formed as by-products in the above reaction are reduced to amines by tin and hydrochloric acid. The amines dissolve in the hydrochloric acid, and the mesitylenic acid remains as a solid residue. Phosphorus pentachloride converts the acid into an acid chloride, and the latter reacts with a cold concentrated aqueous solution of ammonia to form a crystalline amide. A solution of sodium hydroxide and bromine converts the amide to an amine.\*



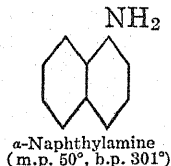
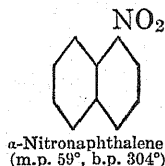
Commercial xylydine, obtained from crude xylene (*o*, *m*, and *p* xylene) by nitration and subsequent reduction, contains all the xylydines except the 1, 3, 5 compound.

### NAPHTHYLAMINES

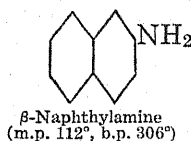
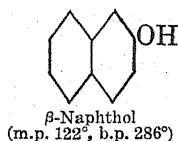
*α-Naphthylamine*,  $\text{C}_{10}\text{H}_7\text{NH}_2$ , crystallizes in the form of needles. It is a colorless compound which has a disagreeable odor. It is very slightly soluble in water, but it dissolves readily in alcohol and ether. With acids it forms salts that are soluble in water, and these salts form blue precipitates when treated with oxidizing agents such as ferric chloride, mercuric nitrate, or chromic acid. *α-Naphthylamine* is made

\* See the Hofmann Rearrangement, p. 431.

from  $\alpha$ -nitronaphthalene by reduction with iron and hydrochloric acid.

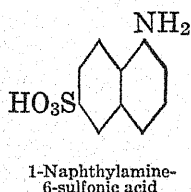
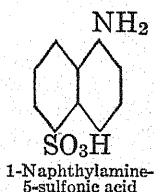
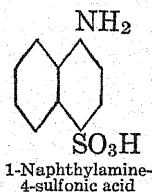


$\beta$ -Naphthylamine,  $C_{10}H_7NH_2$ , crystallizes in pearly plates. It is odorless and practically insoluble in water.  $\beta$ -Naphthol is converted into  $\beta$ -naphthylamine by heating it with zinc chloride and ammonia:



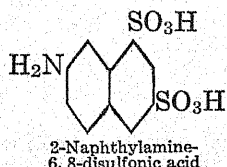
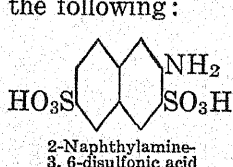
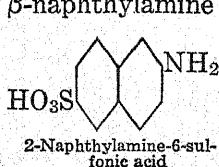
This method can be applied with equal success in the preparation of  $\alpha$ -naphthylamine. Both of these amines are manufactured in large quantities for use in the dye industry.

The naphthylaminesulfonic acids also are used in large quantities in the preparation of dyes. These derivatives may be made by the action of sulfuric acid on the naphthylamines or by reducing nitronaphthalenesulfonic acids. The following sulfonic acids are produced when concentrated sulfuric acid acts on  $\alpha$ -naphthylamine:



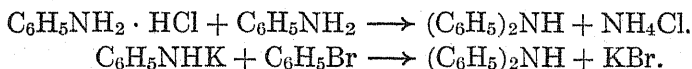
The first member of this group, 1-naphthylamine-4-sulfonic acid, is commonly called naphthionic acid.

Among the more important sulfonic acid derivatives of  $\beta$ -naphthylamine are the following:



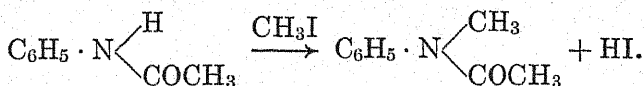
## SECONDARY AMINES

*Diphenylamine*,  $(\text{C}_6\text{H}_5)_2\text{NH}$  (m.p.  $53^\circ$ , b.p.  $302^\circ$ ), a crystalline substance having a pleasant odor, is a typical secondary aromatic amine. It is prepared by heating a mixture of aniline hydrochloride and free aniline, or from bromobenzene and potassium anilide:



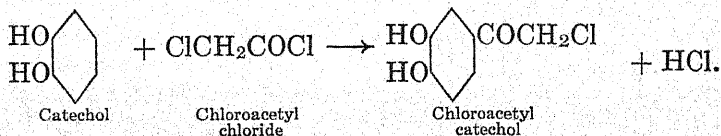
Diphenylamine is oxidized by nitric acid, bromine water, chromic acid, and other oxidizing agents. It yields colored oxidation products — usually blue. Not all these products have been identified.

*Methylaniline*,  $\text{C}_6\text{H}_5\text{NHCH}_3$  (b.p.  $195.7^\circ$ , sp. gr. 0.987), is a yellow liquid, obtained from aniline by replacing one hydrogen atom of the amino group by the methyl radical. This may be accomplished through the direct action of methyl iodide on aniline and subsequent treatment with an alkali, but the product obtained in this way is contaminated with dimethylaniline. To obtain the pure secondary amine the following procedure is adopted. Aniline is boiled with glacial acetic acid to form acetanilide,  $\text{C}_6\text{H}_5 \cdot \text{NH} \cdot \text{CO} \cdot \text{CH}_3$ , which is converted by methyl iodide into methylacetanilide:



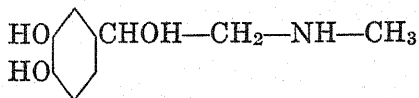
This product is hydrolyzed by boiling it with a solution of sodium hydroxide, and the methylaniline is obtained by extracting with ether or by distilling with steam.

Among the secondary amines that have important therapeutic uses, adrenaline and ephedrine may be mentioned. Adrenaline causes contraction of the small arteries and is used to increase blood pressure. It may be obtained from the suprarenal glands of the horse or it may be synthesized from catechol and chloroacetyl chloride:



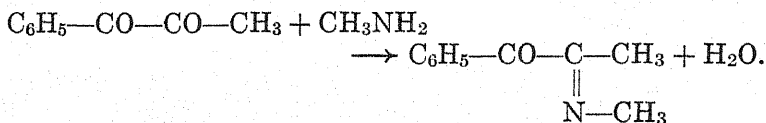


Methylamine reacts with chloroacetyl catechol, forming an amino ketone,  $(\text{OH})_2\text{C}_6\text{H}_3\text{COCH}_2\text{NHCH}_3$ , which is then reduced to adrenaline,

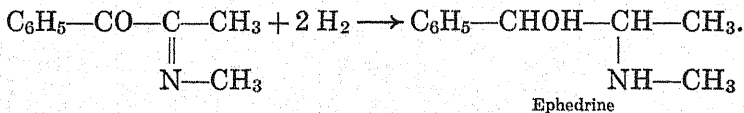


Adrenaline

Ephedrine is used in the treatment of asthma and for other purposes. Methylphenyl diketone reacts with methylamine in alcohol as follows:



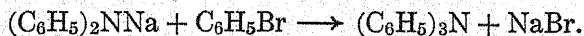
The condensation product is reduced by hydrogen with nickel as a catalyst:



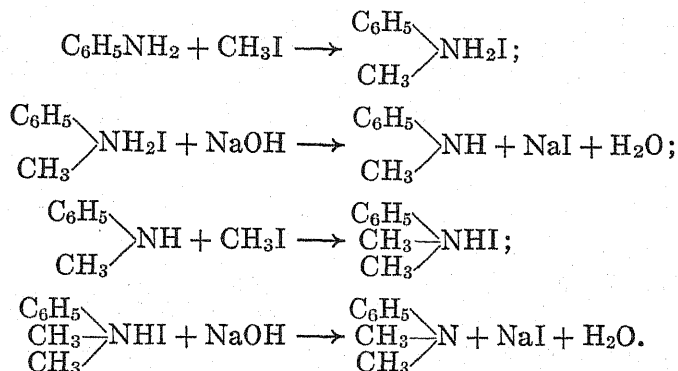
The amine is usually isolated and used in the form of a hydrochloride.

### TERTIARY AMINES

*Triphenylamine*,  $(\text{C}_6\text{H}_5)_3\text{N}$  (m.p.  $126^\circ$ , b.p.  $365^\circ$ ), is a crystalline solid, soluble in acetone and benzene, and practically insoluble in water. It has no basic properties, differing in this respect from the tertiary aliphatic amines. It is prepared by heating diphenylamine and bromobenzene with sodium. A sodium derivative of diphenylamine is the first product formed:



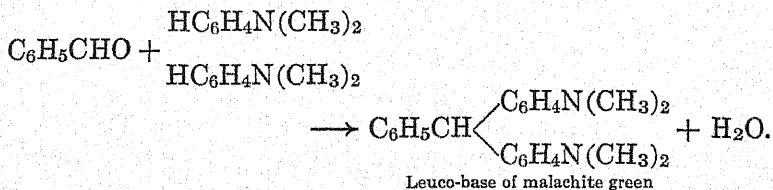
*Dimethylaniline*,  $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2$  (m.p.  $1.7^\circ$ , b.p.  $193.5^\circ$ ), a pale yellow oil having a disagreeable odor, may be prepared from aniline and methyl iodide. An addition product is formed from which hydrogen iodide may be removed by distillation with an alkali. This gives rise to monomethylaniline, and a repetition of the process results in the formation of dimethylaniline:



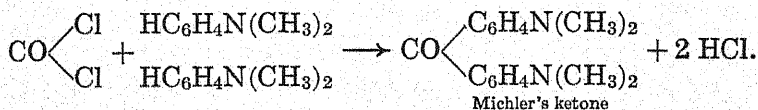
Commercially, the amine is manufactured by heating aniline hydrochloride with methyl alcohol. A mixture of aniline hydrochloride and methyl alcohol heated to  $250^\circ$  in an autoclave gives a mixture of aniline, toluidine, xyloidine, and mesidine. By proper control of the conditions this method may be used in the preparation of almost any one of the possible products. The mechanism of the reaction is discussed under the Hofmann rearrangement.

The *para* hydrogen atom in dimethylaniline is very reactive. As a result, dimethylaniline forms condensation products with a variety of reagents. The following examples are typical:

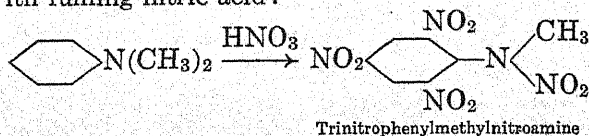
1. With aldehydes:



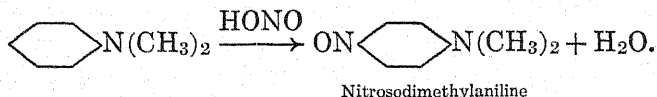
2. With phosgene:



3. With fuming nitric acid:



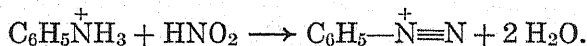
## 4. With nitrous acid :



Nitrosodimethylaniline crystallizes in green plates, melting at 85°. Potassium permanganate oxidizes the nitroso group to a nitro group. All secondary aromatic amines react with nitrous acid, forming nitrosoamines, the NO group being attached to the nitrogen of the amino group; and primary aromatic amines are diazotized by nitrous acid.

## THE DIAZO REACTION

Nitrous acid converts primary aromatic amines into diazonium compounds. The usual procedure for the preparation of these compounds consists in treating a cold aqueous solution of an amine salt with hydrochloric acid and either amyl nitrite or sodium nitrite. The nitrous acid liberated from the nitrite acts upon the amine salt as follows :



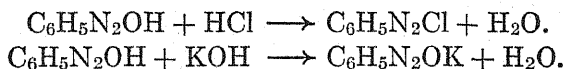
An excess of nitrous acid should be avoided, for it is a fairly active oxidizing agent. Moreover, with some types of compounds — especially secondary and tertiary amines and some phenols — nitroso derivatives are formed. In the manufacture of azo dyes, amines and phenols are used in connection with diazotized primary amines, and in such cases an excess of nitrous acid not only reduces the yield in consequence of undesired reactions, but unnecessarily contaminates the product with other substances, rendering purification difficult and expensive. The sodium nitrite or other source of nitrous acid should be added slowly with constant stirring, until a drop of the mixture produces a blue color on starch-potassium iodide paper.\* The structure assigned to the diazonium salt in the above equation is supported by the following considerations :

1. The group  $\text{—N}_2$  is attached to the ring by one valence bond only, for it is easily replaced by such univalent radicals as OH, CN, and Br.

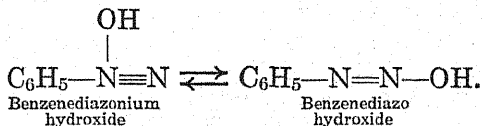
\* Free nitrous acid oxidizes iodide ion to free iodine, which imparts a blue color to starch :  $2 \text{HI} + 2 \text{HNO}_2 \longrightarrow 2 \text{H}_2\text{O} + 2 \text{NO} + \text{I}_2$ .

2. A diazonium compound acts like a salt of a fairly strong base. The ion  $\text{C}_6\text{H}_5\text{N}_2^+$  is comparable to the ammonium group  $\text{NH}_4^+$ . Benzenediazonium chloride, like ammonium chloride, is a neutral salt and a highly ionized compound. With platinum and gold compounds it forms insoluble double salts of the type  $(\text{C}_6\text{H}_5\text{N}_2)_2\text{PtCl}_6$ . Benzenediazonium carbonate, like ammonium carbonate, gives an alkaline reaction in aqueous solution through hydrolysis. In ammonium hydroxide the hydroxyl group is held by the charge on the ammonium ion, and the corresponding diazonium structure should indicate a similar relationship between nitrogen and hydroxyl.

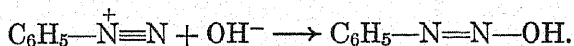
Benzenediazonium hydroxide reacts not only with acids but also with bases. Thus we have two types of reactions:



Hantzsch explained this anomalous behavior by assuming the existence of tautomeric forms:



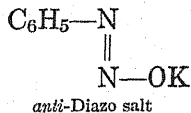
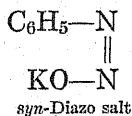
One form contains nitrogen as it exists in ammonium hydroxide. This form is called a diazonium compound. The other form contains trivalent nitrogen only and is designated a diazo compound. A diazonium hydroxide is a strong base; a diazo hydroxide is a weak acid. In acid solution compounds of this kind have the diazonium structure. They form salts that dissociate, yielding ions of type  $\text{C}_6\text{H}_5-\text{N}^+\equiv\text{N}$ . When a base is added the compound assumes the diazo form:



The diazo compounds form salts of the type  $\text{C}_6\text{H}_5-\text{N}=\text{N}-\text{OK}$ . Diazo compounds and diazonium salts react with phenols and with aromatic amines to form the azo dyes. The reaction goes best in alkaline solution.\*

\* If an acid medium is required to hold the reagents in solution, sodium acetate is usually added to reduce the hydrogen ion concentration to that of an acetic acid solution, for coupling does not occur in solutions of high hydrogen ion concentration.

The double bond between nitrogen atoms in the diazo compound gives rise to geometrical isomers which are called *syn* and *anti* compounds:



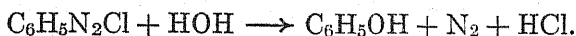
*Anti*-diazo compounds are formed in strongly alkaline solutions only. The *syn*-diazo compounds, when warmed, decompose with an evolution of nitrogen. An important exception to this rule, however, is found in the case of the azo dyes. The so-called coupling reactions with amines and phenols produce stable molecules. Both *syn*-diazo and *anti*-diazo compounds are capable of yielding dyes, but the coupling is usually carried out in dilute solutions of bases, and *syn* compounds are formed. Reduction of an azo dye with stannous or titanous chloride breaks the molecule between the nitrogen atoms, leaving nitrogen attached to each of the aromatic nuclei. This behavior affords further evidence in support of the  $-\text{N}=\text{N}-$  structure of the diazo group.

The *syn*-diazo compounds are more reactive than the *anti*-diazo compounds. They are hydrolyzed more completely, being salts of a weaker acid. The *syn* compounds are more easily reduced to hydrazines and more readily oxidized to nitroamines; they are more soluble and, in the dry state, more explosive than the corresponding *anti*-diazo bodies. Rapid decomposition with evolution of nitrogen is a characteristic property of the *syn* series. The *anti*-diazo compounds yield the same decomposition products, but the change occurs more slowly and requires a higher temperature, the first step, in all probability, being a rearrangement to the *syn* form.

A *syn*-diazo hydroxide has never been isolated, for as soon as liberated from the salt by means of an acid, it either decomposes, yielding a phenol and nitrogen, or changes to the diazonium form. *Anti*-diazo hydroxides have been obtained by treating the corresponding potassium salts with acetic acid at temperatures low enough to prevent rapid rearrangement. They are colorless crystalline compounds, but they are quite unstable and even at low temperatures in aqueous solution they are soon converted into phenols and other products.

Diazonium as well as diazo salts, when dry, are explosive. Detonation is accomplished by percussion or by heat. The important reactions of the diazonium salts are carried out in aqueous solution, and it is therefore unnecessary to assume the risk of an explosion in dealing with these compounds. Transformations of diazonium salts are used in synthetic work to introduce the following radicals and elements into aromatic compounds:

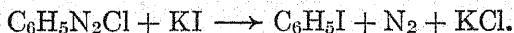
1. *Hydroxyl*. When an aqueous solution of a diazonium salt is heated, nitrogen gas escapes and a phenol is formed:



To obtain a good yield of phenol and to avoid contamination with products formed in side reactions with nitrous acid, it is necessary to make sure (1) that the amine used has been completely diazotized and (2) that no excess of nitrous acid remains in solution. To accomplish the first requirement a slight excess of sodium nitrite is added, and to remove the excess of nitrous acid formed a small quantity of urea is introduced before the mixture is heated. Urea decomposes the nitrous acid according to the equation



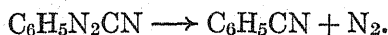
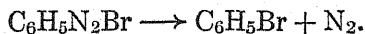
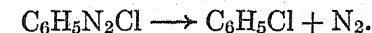
2. *Iodine*. Potassium iodide is added to a solution of the diazonium salt and the mixture is allowed to stand at room temperature several hours. Nitrogen escapes slowly. The mixture is finally heated to complete the reaction:



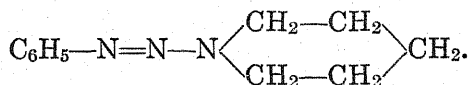
Phenol is formed at the same time through the decomposition of the diazonium salt by water, but the difference in the rates of the two reactions makes it possible to use this method in the preparation of phenyl iodide.

3. *Chlorine, bromine, and cyanogen*. The plan outlined in the last paragraph for the introduction of iodine into the ring does not apply to chlorine, bromine, or cyanogen. Sandmeyer discovered, however, that in the presence of cuprous chloride, bromide, or cyanide the reaction is analogous to the one in which phenyl iodide is formed. Copper powder or fine filings

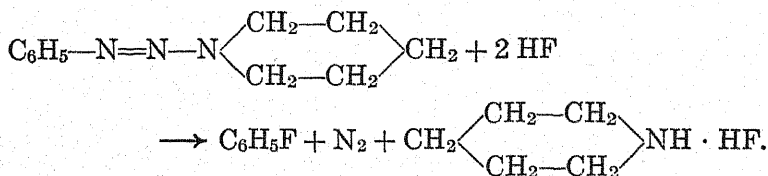
in connection with KCl, KBr, or KCN may be substituted for the cuprous salts. Chlorine, bromine, and the CN group, therefore, may be substituted for the diazo group :



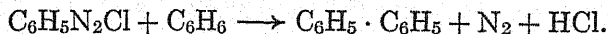
4. *Fluorine*. Free fluorine decomposes benzene, forming hydrogen fluoride and carbon, but diazonium salts react with piperidine to form a stable diazo piperidide,



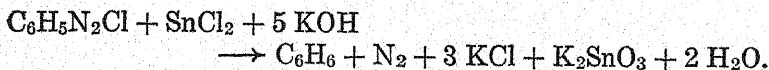
Hydrofluoric acid decomposes this substance, forming fluorobenzene, nitrogen, and piperidine hydrofluoride :



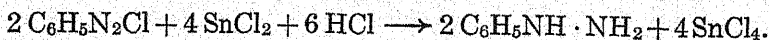
5. *Aryl radicals*. When a dry diazonium salt is dissolved or suspended in benzene or in any other liquid aromatic hydrocarbon and warmed with aluminum chloride, the diazo group is replaced by an aryl radical :



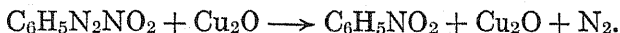
6. *Hydrogen*. An alkaline solution of stannous chloride acts upon a diazonium salt, replacing the diazo group by hydrogen, as shown by the following equation :



In acid solution stannous chloride reduces the compound to a derivative of hydrazine, no nitrogen being evolved :



7. *The NO<sub>2</sub> group.* A primary aromatic amine is converted into a nitro-compound by dissolving the amine in cold dilute nitric acid, adding two equivalents of sodium nitrite, and introducing the solution slowly into a cold aqueous suspension of cuprous oxide:

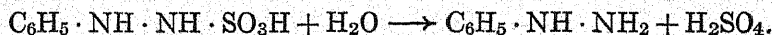
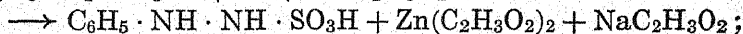
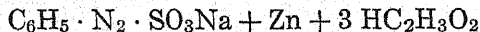
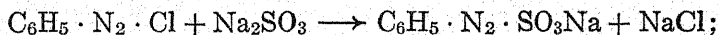


Cuprous oxide is made by dissolving copper sulfate and glucose in hot water and rendering the solution alkaline by the addition of sodium hydroxide. The mixture is then cooled and allowed to stand until the green gelatinous cupric hydroxide has been reduced by the sugar to the yellow cuprous oxide. The excess of alkali is then exactly neutralized by acetic acid.

### HYDRAZINES

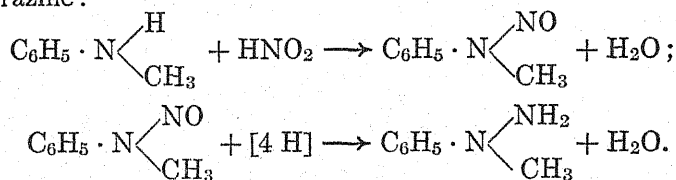
*Hydrazine*,  $\text{H}_2\text{N}-\text{NH}_2$  (m.p.  $1.4^\circ$ , b.p.  $113^\circ$ ), fumes in moist air, forming a hydrate, and dissolves rapidly in cold water, yielding an alkaline solution containing the ions  $\text{N}_2\text{H}_5^+$  and  $\text{OH}^-$ . Hydrazine is made by the electrolytic oxidation of an ammonium salt. A viscous solution of the ammonium salt is required for this purpose, and glue or starch is added to impart this quality to the electrolyte. Some of the derivatives of hydrazine are important reagents, and among these phenylhydrazine is preëminent.

*Phenylhydrazine*,  $\text{C}_6\text{H}_5 \cdot \text{NH} \cdot \text{NH}_2$  (m.p.  $19.6^\circ$ , b.p.  $243.5^\circ$ ), is a colorless, oily liquid which acquires a red color on standing in contact with air. It is slightly soluble in water and soluble in all proportions in alcohol and ether. It is a basic substance. With acids it forms well-crystallized, soluble salts. It is prepared by reduction of a benzenediazonium salt with an acid solution of stannous chloride, or by treating the diazonium salt with sodium sulfite, zinc dust, and acetic acid. When a sulfite is used, the  $\text{SO}_3\text{H}$  group is finally eliminated by boiling with fuming hydrochloric acid. Phenylhydrazine hydrochloride, being almost insoluble in a concentrated solution of hydrochloric acid, is precipitated. This constitutes the usual laboratory procedure.

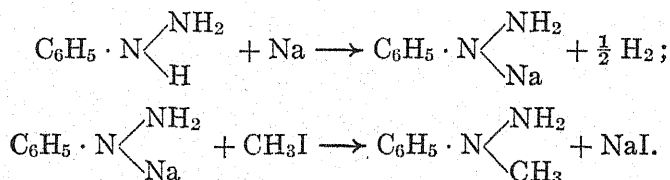




The structure of phenylhydrazine is established by the following reactions: Methylaniline is converted by nitrous acid into a nitrosoamine, which on reduction yields methylphenyl hydrazine:



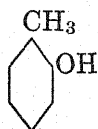
The same product is obtained from phenylhydrazine by treatment with sodium and subsequent removal of the metal by means of methyl iodide:



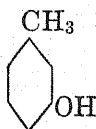
The uses of phenylhydrazine are considered in connection with the general reactions of aldehydes and ketones, and especially with reference to the hydrazones and osazones of the carbohydrates.

## PHENOLS

Phenols are compounds derived from aromatic hydrocarbons by substituting hydroxyl groups for hydrogen atoms in the ring. The aromatic nucleus may be a simple benzene ring, or it may contain condensed rings as found in naphthalene, anthracene, or phenanthrene. The feature that distinguishes a phenol from an aromatic alcohol is the attachment of the hydroxyl group to a carbon atom of the nucleus. It is attached to a side-chain carbon atom in an alcohol. Thus the formula  $C_7H_7OH$  represents three phenols and one alcohol:



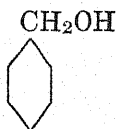
*o*-Cresol



*m*-Cresol



*p*-Cresol



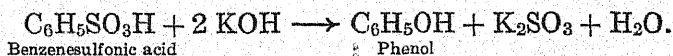
Benzyl alcohol

Phenols are classified as monohydric, dihydric, or polyhydric on the basis of the number of hydroxyl groups attached to the nucleus. The termination *ol* is used to denote the presence of alcoholic as well as phenolic hydroxyl. Thus benzyl alcohol may be called phenyl carbinol, and the hydroxy toluenes are commonly called cresols. The hydroxy derivatives of the xylenes are called xyenols.

Although *phenol* is a general name referring to a class of compounds, it is commonly used to designate a particular compound,  $C_6H_5OH$ , known also as carbolic acid.

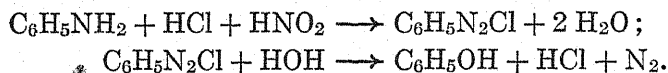
**Preparation.** Coal tar is the principal source of ordinary phenol. Some cresols, xylenols, and related compounds occur with it. Phenols are prepared synthetically in several ways:

1. From sulfonic acids by fusion with a base:\*



\* Sulfanilic acid,  $C_6H_4 \begin{matrix} \nearrow NH_2 (1) \\ \searrow SO_3H (4) \end{matrix}$ , yields aniline and not *para*-aminophenol when fused with an alkali.

2. From aromatic amines through the diazo reaction. Nitrous acid acts upon primary amines, liberating nitrogen and introducing hydroxyl in the place of the  $\text{NH}_2$  group. In the aliphatic series this reaction is used to convert amines into alcohols. Aromatic amines yield phenols. The reactions differ in one respect, namely, in the case of the aromatic amines an intermediate product — a diazonium salt — can be isolated; but when heated with water, the diazonium salt yields nitrogen and a phenol:



3. From aryl halides by hydrolysis. Recent experiments indicate the possibility of preparing phenol from chlorobenzene or bromobenzene by treatment with 8 per cent aqueous sodium hydroxide in a rotating iron or copper bomb kept for an hour at  $325^\circ$  to  $360^\circ$ .\*

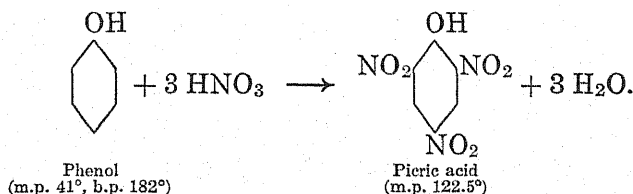
**Properties.** The phenols are colorless, crystalline solids. The lower members have low melting points, characteristic odors, and strong antiseptic properties. They are only slightly soluble in water, the solubilities decreasing rapidly as the molecular weights increase. In alcohol and ether they dissolve readily. They act like weak acids, the hydrogen of the hydroxyl being easily replaced by metals. The resulting phenolates are largely hydrolyzed by water, and are completely decomposed by acids. Carbon dioxide in water furnishes a sufficient concentration of hydrogen ions to regenerate phenol from a phenolate. Phenols are insoluble, therefore, in solutions of carbonates, but they dissolve in dilute solutions of sodium or potassium hydroxide.† The phenyl or any other aryl radical is more negative than an alkyl radical, and consequently an aryl hydroxide (phenol) is more acidic than an alkyl hydroxide (alcohol). The dissociation constant,  $K_a$ , of phenol is about  $1.5 \times 10^{-10}$ . Substitution of chlorine or bromine for hydrogen in positions *ortho* and *para* to the hydroxyl group is easily accomplished in aqueous solution by direct action of the halogen. In this respect the influence of the hydroxyl group is similar to that of the amino group.

\* William J. Hale and Edgar C. Britton, *J. Ind. and Eng. Chem.*, **20**, 114 (1928).

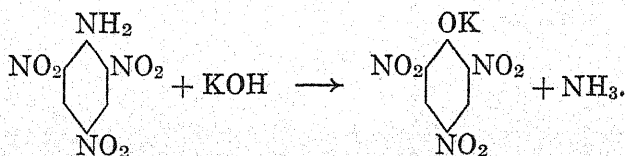
† For exceptions see Torrey and Kipper, *J. Am. Chem. Soc.*, **30**, 836 (1908), and Adams, *J. Am. Chem. Soc.*, **41**, 247 (1919).

*Phenol*,  $\text{C}_6\text{H}_5\text{OH}$  (m.p.  $41^\circ$ , b.p.  $182^\circ$ ), is commonly known as carbolic acid. It dissolves in fifteen times its weight of cold water and forms a crystalline hydrate,  $2\text{C}_6\text{H}_5\text{OH} \cdot \text{H}_2\text{O}$ , melting at  $16^\circ$ . At one time phenol was employed quite extensively in surgery, but safer antiseptics, such as iodine, alcohol, mercuric chloride, and *m*-cresol, have rendered its use in this connection obsolete. Phenol is used in the preparation of salicylic acid, phenacetine, and picric acid. It is used also in the manufacture of bakelite and other synthetic plastics.

*Picric acid*, or trinitrophenol, is obtained by dissolving phenol in concentrated sulfuric acid, then adding concentrated nitric acid and heating the mixture on a steam bath.

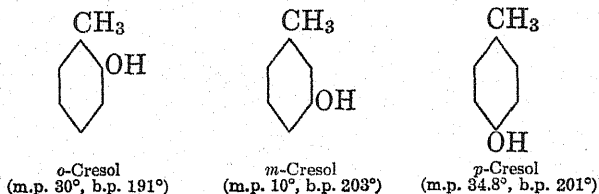


Picric acid is a yellow crystalline compound. It is slightly soluble in cold water and the solution has a very bitter taste. The salts of picric acid are used in the manufacture of explosives. They are detonated by percussion. The nitro groups enhance the acidic properties of the phenol to such an extent that picric acid is stronger than acetic acid. The trinitrophenyl radical is a negative group comparable to an acyl radical. Phosphorus pentachloride converts picric acid into picryl chloride, a crystalline solid that melts at  $83^\circ$ . The chloride is readily hydrolyzed. Picryl chloride,  $(\text{NO}_2)_3\text{C}_6\text{H}_2\text{Cl}$ , acts like an acid chloride. Picramide,  $(\text{NO}_2)_3\text{C}_6\text{H}_2\text{NH}_2$ , is made from picryl chloride by treatment with ammonia just as any amide is made from an acid chloride. Picramide acts much like an amide of a carboxylic acid. It is hydrolyzed by a hot solution of an alkali.



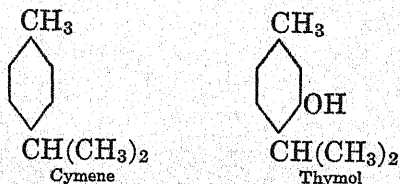
## CRESOLS

According to the structure theory, there should be three cresols, or hydroxy toluenes. Three such compounds are known. They are all obtained from the creosote oil produced in the distillation of coal tar :



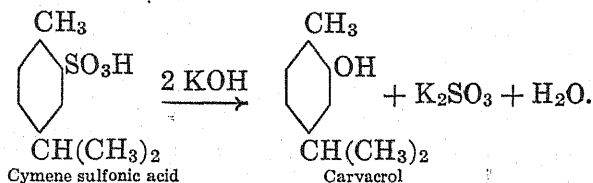
In physical properties the cresols resemble each other so closely that they cannot be separated and purified by fractional distillation and crystallization. Each may be prepared in a pure state from the corresponding toluidine by means of the diazo reaction. *p*-Cresol is a decomposition product of some proteins and is found in the form of a sulfonic acid in urine. The cresols are decomposed by hot chromic acid or other vigorous oxidizing agents, unless the hydrogen of the hydroxyl group has been replaced by an alkyl or acyl group. When the alkyl or acyl derivative is oxidized, the methyl group is converted to carboxyl. The hydroxyl group may then be restored by hydrolysis.

*Thymol*, a constituent of the essential oils of thyme and mint, is obtained from the plants by extraction with aqueous sodium hydroxide, from which it is precipitated by neutralizing the base. It forms large colorless crystals (m.p. 51.5°) only slightly soluble in water (1 : 1100). It is volatile with steam and very soluble in alcohol and ether. Unlike phenol and the cresols, thymol in aqueous solution fails to develop a color in the presence of ferric chloride, and with bromine water only a faint turbidity is produced. It is a hydroxy derivative of the hydrocarbon *cymene* (*paramethylisopropylbenzene*).



Thymol is used, to some extent, as an antiseptic. It is less toxic to bacteria than is phenol but it is said to be more effective than phenol in preventing the growth of molds and other fungi.

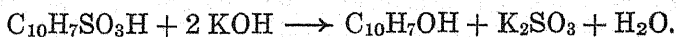
*Carvacrol* (m.p. 1°) is isomeric with thymol, which it resembles in chemical and physical properties. Carvacrol is obtained by fusing cymene sulfonic acid with potassium hydroxide:



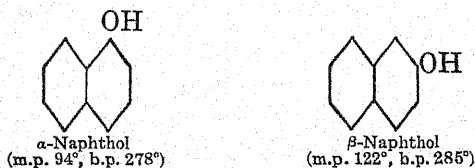
The position of the hydroxyl group is established by the fact that when carvacrol is heated with phosphorus pentoxide, *o*-cresol and propylene are the products formed.

### NAPHTHOLS

The monohydroxy derivatives of naphthalene are known as naphthols. These compounds are of great importance on account of their use in the manufacture of dyes. They are prepared from the naphthalenesulfonic acids by fusion with potassium hydroxide, or from the naphthylamines by the diazo reaction:

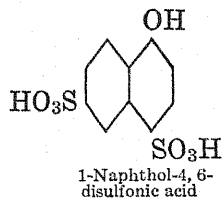
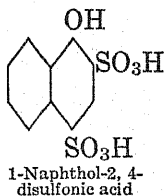
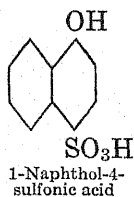


The naphthols have the following structures:

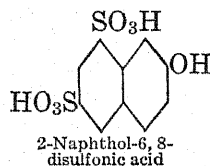
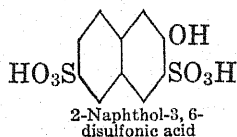
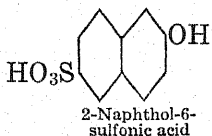


They form colorless, monoclinic crystals, almost insoluble in water, but readily soluble in alcohol, benzene, ether, and chloroform. When heated with ammonia they are converted into naphthylamines. The naphthols are oxidized by ferric chloride to dinaphthols,  $\text{HO} \cdot \text{C}_{10}\text{H}_6 \cdot \text{C}_{10}\text{H}_6 \cdot \text{OH}$ . At the same time iron salts of these compounds are formed, giving colored solutions and colored precipitates.  $\alpha$ -Naphthol yields a violet and  $\beta$ -naphthol a green oxidation product.

Sulfuric acid acts upon the naphthols, producing substitution products known as naphtholsulfonic acids. Some of these are used in large quantities in the manufacture of dyes. The following derivatives of  $\alpha$ -naphthol are valuable representatives of the series:

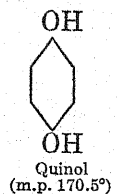
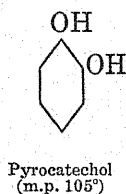


Among the sulfonic acids of technical value derived from  $\beta$ -naphthol are the following:



### DIHYDRIC PHENOLS

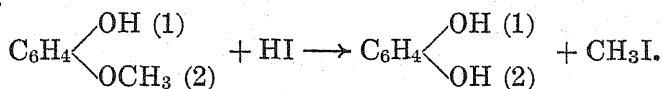
There are three dihydroxy derivatives of benzene:



*Pyrocatechol* is obtained from several natural sources, including sugar beets, the leaves of wild grapes, and many resins. It is prepared synthetically by fusing *o*-phenolsulfonic acid or *o*-bromophenol\* with potassium hydroxide. It is easily made

\* *Orthochlorophenol*, the chief product formed in the direct chlorination of phenol, is cheaper than the corresponding bromine and iodine derivatives. But the product formed by fusion of the chlorophenol with alkali is a mixture of *ortho* and *meta* dihydroxy benzenes, and principally the *meta* compound, resorcinol. It is not uncommon for an *ortho* or a *para* disubstitution product of benzene to yield *meta* dihydroxy benzene when fused with an alkali. The higher the fusion temperature the greater will be the yield of the *meta* compound. The identification of a compound formed in a reaction involving fusion with a base does not determine the orientation of groups that were present in the molecule before fusion.

from guaiacol,  $C_6H_4(OH)(OCH_3)$ , by heating with hydriodic acid:



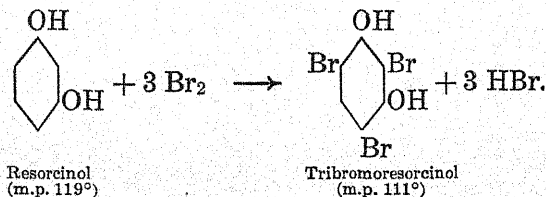
Guaiacol is obtained from the creosote oil fraction of beechwood tar. It is a crystalline substance (m.p.  $28.5^\circ$ , b.p.  $205^\circ$ ), having a pleasant odor and a sweet taste. Ferric chloride acts upon a dilute alcoholic solution of guaiacol, giving an immediate blue color, which gradually changes to green and finally yellow. When heated with zinc dust, guaiacol yields anisol,  $C_6H_5OCH_3$  (m.p.  $-37.3^\circ$ , b.p.  $155.8^\circ$ ).

Pyrocatechol in alkaline solution absorbs oxygen from the air. It precipitates gold, silver, and platinum from their salts. This property makes it useful as a photographic developer, and it is sold for this purpose under the names *catechol* and *pyrocatechin*.

*Resorcinol*, resorcin, or *m*-dihydroxybenzene, is made by heating *m*-benzenedisulfonic acid or *p*-chlorobenzenesulfonic acid with sodium hydroxide.

Resorcinol is used in the manufacture of fluoresceine and other dyes. When heated with sodium nitrite, it yields the deep blue dye lacmoid, which turns red in the presence of hydrogen ions and is used as an indicator. Resorcinol forms a violet-colored compound with ferric chloride. Lead acetate does not precipitate this phenol from aqueous solution — a test used to distinguish it from pyrocatechol. It differs from pyrocatechol also in being a much weaker reducing agent. It is, however, active enough as a reducing agent to precipitate cuprous oxide from Fehling's solution and metallic silver from an ammoniacal solution of silver oxide.

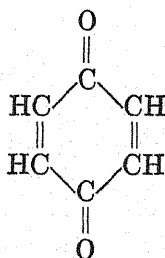
Resorcinol crystallizes from benzene in large colorless needles. It is very soluble in water (147 g. in 100 g. of water at  $12.5^\circ$ ). It reacts with bromine water, immediately precipitating tribromoresorcinol:



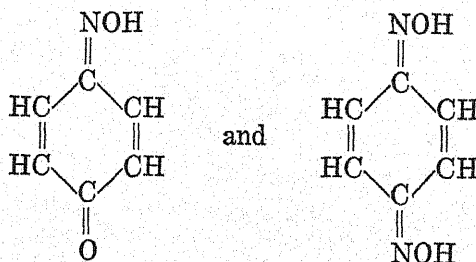


*Quinol*, hydroquinone, or *p*-dihydroxybenzene is used extensively as a photographic developer. In reducing power it stands between catechol and resorcin. Oxidizing agents convert it into a yellow crystalline compound, known as quinone. Hydroquinone crystallizes from water in colorless prisms. Its solubility in water at room temperature is about six parts per hundred.

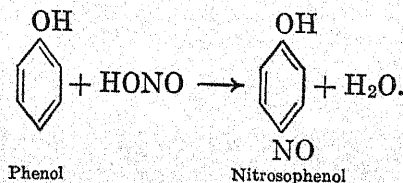
*Quinone*. The yellow crystalline compound known as quinone is an important oxidation product of hydroquinone, of *p*-aminophenol, of *p*-sulfanilic acid, and of many other *para* disubstitution products of benzene. Its empirical formula is  $C_6H_4O_2$ , and its genetic relationship to the compounds mentioned above leads to the assumption that its structure is



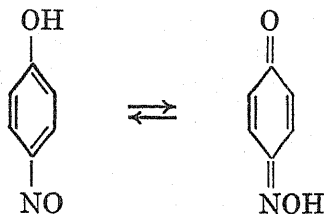
The existence of carbonyl groups in quinone is indicated also by the fact that, with hydroxylamine, quinone yields a monoxime and a dioxime,



The monoxime is identical with nitrosophenol, a compound formed by the action of nitrous acid on phenol:



A tautomeric equilibrium exists between the two forms:



Oxidation of hydroquinone changes the structure of the ring from the benzoid to the quinoid form:

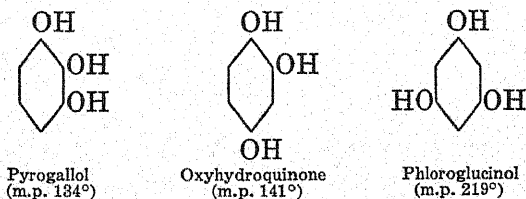


Practically all compounds having the quinoid structure are colored. It has been customary to attribute to this structure the color of quinone. The change in structure, however, is only one of the results attending the oxidation. There may be a more fundamental cause for the display of color.

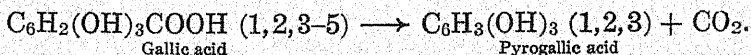
Quinone,  $C_6H_4O_2$ , forms an addition product with unoxidized molecules of quinol, yielding quinhydrone,  $C_6H_4O_2 \cdot C_6H_4(OH)_2$ . Ferric chloride carries the oxidation to this stage and the quinhydrone precipitates in the form of red prisms, having a fine green metallic luster. The nature of the tie between quinone and hydroquinone in quinhydrone is not definitely known.

### TRIHYDRIC PHENOLS

There are three trihydroxy derivatives of benzene:



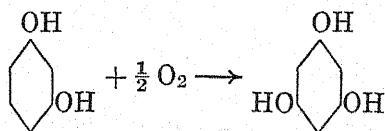
*Pyrogallol*, pyrogallic acid, or 1,2,3-trihydroxybenzene, was first obtained by distilling gallic acid:



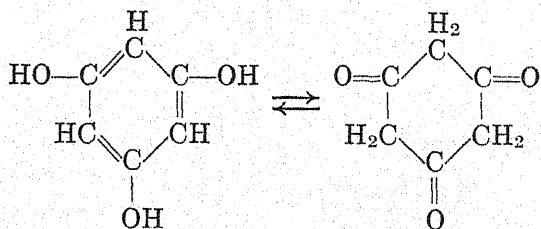
It crystallizes in soft, white leaflets and dissolves in about twice its weight of water. It is a mild poison. An alkaline solution of this phenol absorbs oxygen rapidly, the solution at the same time acquiring a brown or black color. It is used as an absorbent for oxygen in gas analysis. It is employed also as a photographic developer.

*Oxyhydroquinone*, 1,3,4-trihydroxybenzene, is prepared from hydroquinone by fusion with sodium hydroxide. The introduction of a hydroxyl group in this manner has been accomplished in many similar cases; the preparation of phloroglucin affords another example (see also Alizarin). The phenol crystallizes from ether in microscopic plates. It has no unusual properties nor important uses.

*Phloroglucinol*, phloroglucin, 1,3,5-trihydroxybenzene, was first obtained from phloridzin, a glucoside occurring in the roots and bark of many trees. It is now made by heating resorcin with sodium hydroxide. Oxygen is absorbed from the air by the fused alkaline mixture.

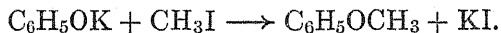


Phloroglucin exhibits the properties of ketones as well as of phenols. It reacts with hydroxylamine, yielding a trioxime, and on the other hand it combines with three molecules of phenylisocyanate, yielding  $\text{C}_6\text{H}_3(\text{O} \cdot \text{CO} \cdot \text{NH} \cdot \text{C}_6\text{H}_5)_3$ , indicating the presence of three hydroxyl groups. The compound exists in tautomeric forms as follows:

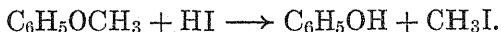


Sodium amalgam acts rapidly upon an aqueous solution of the compound, introducing six hydrogen atoms with the formation of the completely saturated hexahydrophloroglucin.

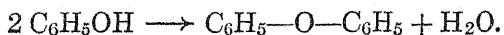
Aromatic ethers are derivatives of the phenols. *Anisol*,  $\text{C}_6\text{H}_5\text{OCH}_3$ , is made by warming a mixture of potassium phenolate and methyl iodide:



Anisol is a liquid. At its boiling point,  $155^\circ$ , it is decomposed by hydrogen iodide:



The ethers in which both radicals are aromatic are made by the action of dehydrating agents on the corresponding phenols. Aryl halides will not react with phenolates. Diphenyl ether,  $\text{C}_6\text{H}_5\text{—O—C}_6\text{H}_5$  (m.p.  $26.9^\circ$ , b.p.  $259^\circ$ ), is made by heating phenol with zinc chloride:



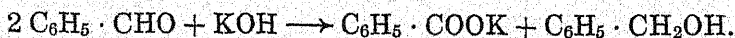
## ALCOHOLS, ALDEHYDES, AND KETONES

### ALCOHOLS

The aromatic alcohols are colorless liquids and solids derived from aromatic hydrocarbons by substituting a hydroxyl group for hydrogen in a side chain. Or they may be regarded as derivatives of the aliphatic alcohols in which hydrogen atoms of the alkyl radicals have been replaced by aromatic radicals. Benzyl alcohol,  $\text{C}_6\text{H}_5 \cdot \text{CH}_2\text{OH}$ , is a typical primary alcohol. Diphenyl carbinol,  $\text{C}_6\text{H}_5 \cdot \text{CHOH} \cdot \text{C}_6\text{H}_5$ , and triphenyl carbinol,  $(\text{C}_6\text{H}_5)_3\text{COH}$ , are examples of secondary and tertiary aromatic alcohols.

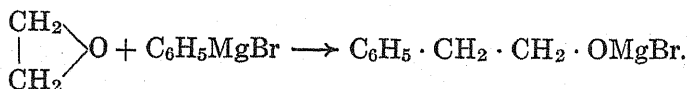
The primary alcohols may be prepared by reduction of the corresponding aldehydes or by the action of silver hydroxide or potassium hydroxide on compounds having halogen atoms in side chains. Secondary alcohols are usually made from ketones by reduction; and tertiary aromatic alcohols are obtained by oxidizing hydrocarbons having three aryl groups attached to the same carbon atom, or by the action of alkalis on tertiary halogen derivatives of the hydrocarbons. Secondary and tertiary alcohols are readily prepared from aldehydes and ketones, respectively, by means of the Grignard reaction.

*Benzyl alcohol*,  $\text{C}_6\text{H}_5 \cdot \text{CH}_2\text{OH}$  (b.p.  $206^\circ$ ), is a colorless liquid having a faint, pleasant odor. On standing exposed to the air it acquires the odor of almond oil owing to the formation of benzaldehyde. In the form of esters of acetic, benzoic, cinnamic, and salicylic acids it occurs in many fragrant flowers and in resins and balsams. It is used extensively in the preparation of artificial perfumes. It is readily prepared by reducing benzaldehyde with sodium amalgam and water or by shaking, for several hours, a mixture of equal volumes of benzaldehyde and a cold saturated aqueous solution of potassium hydroxide. In the latter process half of the benzaldehyde is oxidized to benzoic acid and half is reduced to benzyl alcohol:



Benzyl alcohol is isomeric with the cresols, but differs from them in being less soluble in alkalies, in the ease with which it is oxidized, and in the character of the oxidation products.

*Phenylethyl alcohol*,  $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{OH}$  (b.p.  $221^\circ$ ), is made from ethylene oxide and phenyl magnesium bromide.



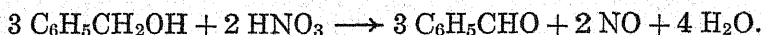
The addition product is hydrolyzed by cold water, yielding phenylethyl alcohol, magnesium hydroxide, and magnesium bromide. The alcohol acquires the odor of hyacinths when exposed to air, owing to the formation of phenylacetic aldehyde.

### ALDEHYDES

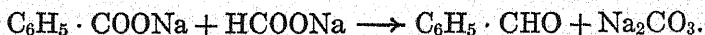
The most important aromatic aldehydes are those having the group  $-\text{CHO}$  attached directly to the benzene ring. Those having the  $-\text{CHO}$  group attached to carbon in a side chain behave, in all respects, like aliphatic aldehydes. The aromatic aldehydes resemble their aliphatic analogues in reactions with phenylhydrazine, hydroxylamine, hydrogen cyanide, and with most oxidizing and reducing agents, but those having the  $-\text{CHO}$  group attached to carbon of the nucleus differ from the aliphatic compounds in their behavior toward ammonia, strong bases, and Fehling's solution. The typical reactions of this group will be considered in connection with benzaldehyde.

The aromatic aldehydes are prepared by the following general methods:

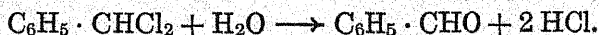
1. Oxidation of a primary aromatic alcohol. In some cases dilute nitric acid can be used for this purpose.



2. Application of heat to a mixture composed of the salt of an aromatic acid and a formate.

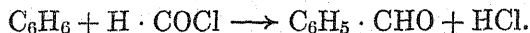


3. Hydrolysis of a compound having the group  $-\text{CHCl}_2$  attached to the ring.



This is accomplished by heating the chloride under pressure with a solution of sulfuric acid or of calcium hydroxide.

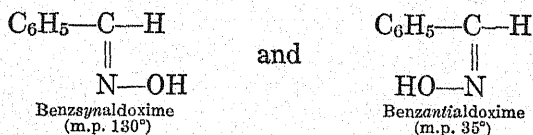
4. The action of carbon monoxide and hydrogen chloride on an aromatic hydrocarbon. Dry cuprous chloride and aluminum bromide are used as catalysts (Gattermann's reaction). Formyl chloride,  $\text{H} \cdot \text{COCl}$ , probably is formed through the union of the two gases.



*Benzaldehyde*,  $\text{C}_6\text{H}_5 \cdot \text{CHO}$  (m.p.  $-56^\circ$ , b.p.  $179.5^\circ$ ), is a colorless oily liquid having the odor of bitter almond oil. It is present in bitter almonds and in cherry kernels in the form of a glucoside called amygdalin. Amygdalin has the empirical formula  $\text{C}_{20}\text{H}_{27}\text{NO}_{11}$ . On hydrolysis it yields benzaldehyde, glucose, and hydrocyanic acid.

Benzaldehyde is made, commercially, by oxidizing toluene with 65 per cent sulfuric acid and powdered manganese dioxide at  $40^\circ$ . It may be made by any of the general methods listed above.

Benzaldehyde reduces an ammoniacal solution of silver hydroxide, but fails to reduce Fehling's solution. Concentrated aqueous solutions of alkalis change benzaldehyde into benzoic acid and benzyl alcohol. This is an example of the Cannizzaro reaction. With ammonia benzaldehyde forms hydrobenzamide,  $(\text{C}_6\text{H}_5 \cdot \text{CH})_3\text{N}_2$ . It reacts with hydroxylamine, yielding benzaldoxime, a compound that exists in two stereoisomeric forms. As obtained in this reaction the oxime is in the form of prismatic crystals which melt at  $35^\circ$ . By treatment with hydrochloric acid (which forms a salt of the oxime) and subsequent removal of the acid by means of sodium carbonate, the oxime is obtained in the form of slender needles melting at  $130^\circ$ . We have here an example of geometrical isomerism. The two oximes have the formulas



The *syn* compound, that is, the one having the hydrogen and hydroxyl on the same side of the molecule, melts at the lower temperature. It reacts with acetic anhydride forming an acetyl

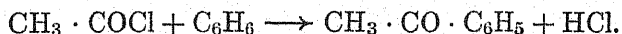
derivative from which the original oxime may be obtained by hydrolysis. When the *anti* compound is warmed with acetic anhydride, a molecule of water is eliminated from the oxime molecule, and phenyl cyanide is produced. The fact that water is easily removed from the high-melting oxime led the early chemists to assign the *syn* structure to this compound. It is now known that the *anti* structure is the one from which phenyl cyanide is obtained. The oximes formerly called *syn* compounds are now regarded as having the *anti* structure, and vice versa.

### KETONES

The aromatic ketones are prepared by the following methods :

1. The action of an acid chloride on an aromatic hydrocarbon in the presence of aluminum chloride.
2. The distillation of a salt or a mixture of salts of aromatic acids.
3. The oxidation of an aromatic secondary alcohol.

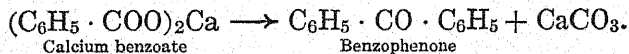
*Acetophenone*,  $\text{CH}_3 \cdot \text{CO} \cdot \text{C}_6\text{H}_5$  (m.p.  $20^\circ$ , b.p.  $202^\circ$ ), is a typical example of the mixed aliphatic-aromatic ketones. It is a crystalline compound having an agreeable odor. It is used in medicine as a soporific and is dispensed under the name of *hyppnone*. It is usually made by treating a mixture of benzene and acetyl chloride with dry aluminum chloride :



A special method for making acetophenone by passing the mixed vapors of acetic acid and benzoic acid over thorium oxide at  $450^\circ$  is also practical.

*Benzophenone*,  $\text{C}_6\text{H}_5 \cdot \text{CO} \cdot \text{C}_6\text{H}_5$  (m.p.  $48.5^\circ$ , b.p.  $306.1^\circ$ ), a colorless crystalline compound, is practically insoluble in water but fairly soluble in alcohol and in ether. It dissolves in sulfuric acid and precipitates unchanged when the acid is diluted with water. It is readily nitrated and chlorinated.

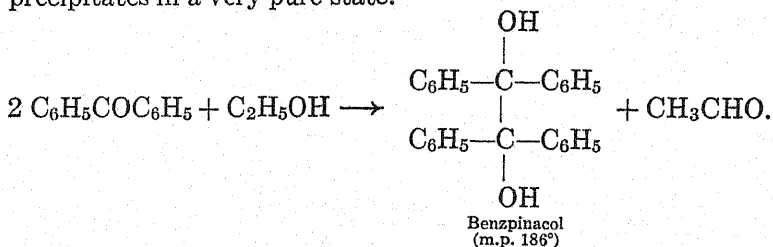
Benzophenone may be prepared by heating benzoyl chloride and benzene with aluminum chloride or by distilling a salt of benzoic acid :





Sodium amalgam, or zinc and potassium hydroxide, may be used on alcoholic solutions of benzophenone for the preparation of benzhydrol,  $\text{C}_6\text{H}_5 \cdot \text{CHOH} \cdot \text{C}_6\text{H}_5$ , a secondary alcohol which crystallizes in needles, melting at  $68^\circ$ . Red phosphorus and hydrogen iodide reduce the ketone to the corresponding hydrocarbon, diphenylmethane.

When a saturated solution of benzophenone in 50 per cent alcohol is exposed to the ultraviolet rays of a mercury vapor arc lamp, the ketone is reduced by the alcohol to benzpinacol. The reduction product is less soluble than the ketone and it precipitates in a very pure state.



Benzophenone exists in four forms, having the following melting points:  $\alpha$ -benzophenone,  $48.5^\circ$ ;  $\beta$ -benzophenone,  $26.5^\circ$ ;  $\gamma$ -benzophenone,  $45^\circ$ – $48^\circ$ ;  $\delta$ -benzophenone,  $-51^\circ$ . The only stable modification under ordinary temperature conditions is the one that melts at  $48.5^\circ$ .

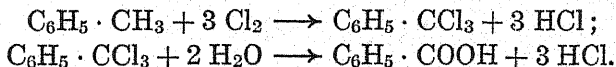
Like other ketones, benzophenone reacts with phosphorus pentachloride, hydroxylamine, phenylhydrazine, and the alkyl and aryl magnesium halides. Some of these reactions are outlined in later chapters.

## AROMATIC ACIDS AND THEIR DERIVATIVES

The principal methods for preparing the aromatic acids are the following:

1. Oxidation of aromatic hydrocarbons having one or more side chains.
2. Oxidation of aromatic alcohols and aldehydes.
3. Hydrolysis of nitriles.

*Benzoic acid*,  $\text{C}_6\text{H}_5 \cdot \text{COOH}$  (m.p.  $121.7^\circ$ , b.p.  $249.2^\circ$ ), is a colorless crystalline compound which occurs in many resins and particularly in gum benzoin. It has been isolated from cranberries and some other fruits. It is found in coal tar also. On a commercial scale it is made by chlorinating hot toluene, then hydrolyzing the resulting benzotrichloride by boiling it with water and calcium hydroxide:



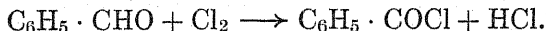
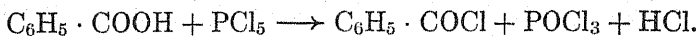
Benzoic acid is only slightly soluble in cold water (1 : 144 at  $20^\circ$ ). It is twenty times as soluble in boiling water. It is volatile with steam and is usually purified by distillation with steam. When the dry acid is heated with lime, it yields benzene and carbon dioxide.

The sodium salt of benzoic acid has mild antiseptic properties. It has been used extensively as a preservative for foods. The pure food law permits this practice if the amount of sodium benzoate used is specified on the label of the container.

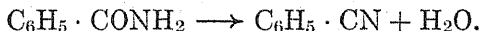
*Benzoyl chloride*,  $\text{C}_6\text{H}_5 \cdot \text{COCl}$  (b.p.  $197.2^\circ$ ), is a colorless liquid with a disagreeable odor. Its fumes have an irritating effect upon the eyes, causing tears.

The benzoyl group,  $\text{C}_6\text{H}_5\text{CO}-$ , may be substituted for hydrogen in a hydroxyl or an amino group by mixing an alcohol, a phenol, or an amine with benzoyl chloride (Schotten-Baumann reaction). The reaction is promoted by the presence of an alkali, which absorbs the liberated halogen acid.

Benzoyl chloride is made by treating benzoic acid with phosphorus pentachloride or by the action of chlorine on benzaldehyde:

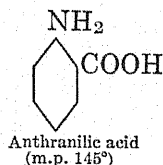
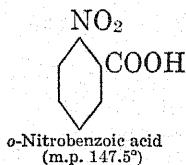


*Benzamide*,  $\text{C}_6\text{H}_5 \cdot \text{CONH}_2$  (m.p.  $130^\circ$ ), is obtained from benzoyl chloride through the action of ammonia. It is soluble in hot water, but precipitates in the form of colorless plates when the solution is cooled. It acts like a weak acid, dissolving readily in alkaline solutions, with the formation of salts of the type  $\text{C}_6\text{H}_5 \cdot \text{CONHM}$  ( $M = \text{metal}$ ). When benzamide is heated with phosphorus pentoxide, benzonitrile is formed:

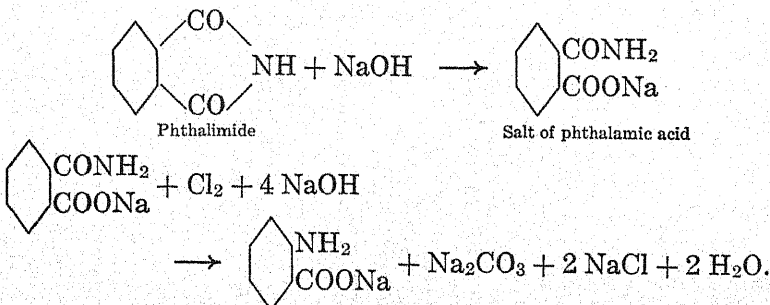


*Nitrobenzoic acids.* *m*-Nitrobenzoic acid is prepared by the direct action of nitric acid on benzoic acid. It crystallizes in plates melting at  $141^\circ$ . The *o*-nitrobenzoic and *p*-nitrobenzoic acids are made from the corresponding nitrotoluenes by oxidation with potassium permanganate. *o*-Nitrobenzoic acid has a sweet taste. The *meta* compound and *para* compound are bitter.

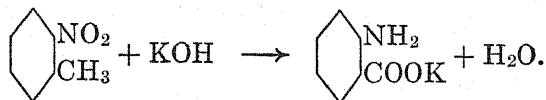
*Anthranilic acid*, *o*-aminobenzoic acid,  $\text{C}_7\text{H}_7\text{NO}_2$ , is obtained from *o*-nitrobenzoic acid by reduction with tin and hydrochloric acid.



On a commercial scale it is made from phthalimide by hydrolysis to phthalamic acid and subsequent treatment with chlorine and sodium hydroxide.

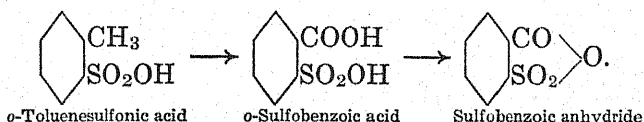


Another interesting synthesis of anthranilic acid is accomplished by boiling *o*-nitrotoluene with a solution of potassium hydroxide. An intramolecular oxidation and reduction occurs.

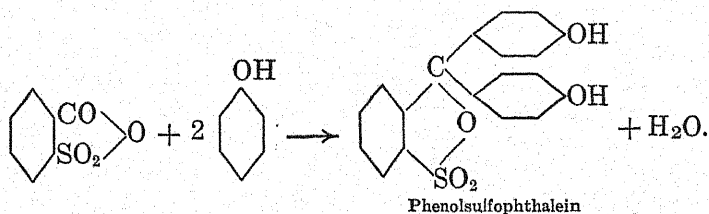


Anthranilic acid is soluble in water and in alcohol. It has a sweet taste. Its methyl ester has an agreeable odor resembling that of orange blossoms. It is used in the manufacture of perfumes.

*Sulfobenzoic acid.* *o*-Sulfobenzoic acid is made by oxidizing *o*-toluenesulfonic acid. It is a colorless crystalline compound melting at 141°. At higher temperatures it gradually loses water and forms an anhydride.

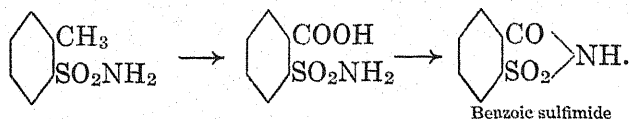


The anhydride combines with phenol when a mixture of the two reagents is warmed with zinc chloride. The resulting compound, phenolsulfophthalein, is a valuable indicator in the determination of hydrogen ion concentrations (see also Phenolphthalein, p. 281).



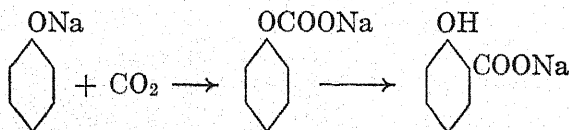
A derivative of sulfobenzoic acid, known as saccharin, is manufactured in large amounts. It is approximately five hundred times as sweet as cane sugar, and although it has no dietetic value, it is used extensively as a substitute for sugar. It is made by oxidizing the amide of *o*-toluenesulfonic acid with potassium permanganate. The amide of *o*-sulfobenzoic

acid is the oxidation product, but when heated it yields water and benzoic sulfimide, or saccharin :



*Salicylic acid*, or *o*-hydroxybenzoic acid,  $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{COOH}$ , occurs in nature as a constituent of the glucoside salicin, in the bark and leaves of the willow. The methyl ester of salicylic acid,  $\text{HOC}_6\text{H}_4\text{COOCH}_3$ , is present in oil of wintergreen. The ester is made in large quantities for use in the manufacture of artificial flavors and perfumes.

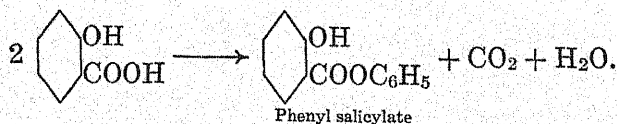
Salicylic acid is made commercially by heating sodium phenolate with carbon dioxide under ten atmospheres of pressure. At  $100^\circ$  the carbon dioxide is absorbed, forming sodium phenyl carbonate. At  $120^\circ$ – $140^\circ$  sodium salicylate is formed :



It may be prepared also by fusing *o*-sulfobenzoic acid with potassium hydroxide or by the action of nitrous acid on anthranilic acid.

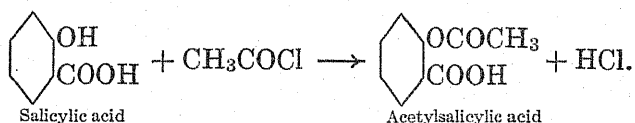
Salicylic acid is soluble in hot water. It crystallizes from water in colorless needles, melting at  $159^\circ$ . With ferric chloride, in neutral solution, it acquires a violet color. This color test distinguishes *o*-hydroxybenzoic acid from the corresponding *meta* and *para* compounds.

When dry salicylic acid is heated with lime, it yields phenol and carbon dioxide. When heated alone to  $160^\circ$ – $200^\circ$ , it yields phenyl salicylate, carbon dioxide, and water :



Phenyl salicylate is used in medicine and is dispensed under the name of *salol*. It is usually prepared by heating a mixture

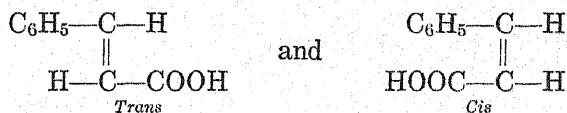
of sodium salicylate, sodium phenolate, and phosphorus oxychloride. Acetylsalicylic acid, commonly called *aspirin*, is another derivative of hydroxybenzoic acid that has therapeutic value. It is made by heating salicylic acid with acetyl chloride or with acetic anhydride:



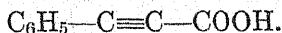
Other derivatives are used in the manufacture of dyes and in the synthesis of perfumes. The annual production of salicylic acid in the United States exceeds 3000 tons.

*Cinnamic acid*,  $\text{C}_6\text{H}_5 \cdot \text{CH} : \text{CH} \cdot \text{COOH}$ , is an example of the type of aromatic acids having the carboxyl group in an unsaturated side chain. Benzaldehyde reacts with an acetate in the presence of acetic anhydride, forming cinnamic acid (see Perkin's reaction, p. 415).

Two stereochemical structures are possible for the acid:



Four modifications of cinnamic acid are known. Ordinary cinnamic acid (m.p.  $133^\circ$ ) has the *trans* structure. The *cis* formula has to be assigned to the other three acids — allocinnamic acid (m.p.  $68^\circ$ ), and two isocinnamic acids, one melting at  $58^\circ$  and the other at  $42^\circ$  — for these three forms are all obtained by reduction of phenylpropionic acid,



This constitutes an interesting case of trimorphism. The compound has a definite and constant chemical structure, but it crystallizes in three different forms. It can be made to crystallize in either of the three forms by inoculating the molten mass with a small crystal of the desired kind.

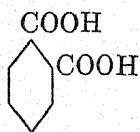
The dissociation constants of a few aromatic acids are shown in the table on the next page. For a definition of  $K_a$ , see page 81.

## DISSOCIATION CONSTANTS

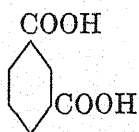
| ACID                                     | $K_a$                 | PER CENT IONIZED IN<br>A 0.1 M SOLUTION |
|--|-----------------------|---|
| $C_6H_5COOH$ . . . . .                   | $6.1 \times 10^{-4}$  | 7.84                                    |
| $ClC_6H_4COOH$ (o) . . . . .             | $1.32 \times 10^{-3}$ | 11.29                                   |
| $ClC_6H_4COOH$ (m) . . . . .             | $1.55 \times 10^{-4}$ | 3.87                                    |
| $ClC_6H_4COOH$ (p) . . . . .             | $9.3 \times 10^{-5}$  | 3.05                                    |
| $BrC_6H_4COOH$ (o) . . . . .             | $1.45 \times 10^{-3}$ | 12.04                                   |
| $BrC_6H_4COOH$ (m) . . . . .             | $1.37 \times 10^{-4}$ | 3.70                                    |
| $HOC_6H_4COOH$ (o) . . . . .             | $1.02 \times 10^{-5}$ | 1.01                                    |
| $HOC_6H_4COOH$ (m) . . . . .             | $8.7 \times 10^{-5}$  | 2.94                                    |
| $HOC_6H_4COOH$ (p) . . . . .             | $2.8 \times 10^{-5}$  | 1.67                                    |
| $NO_2C_6H_4COOH$ (o) . . . . .           | $6.16 \times 10^{-3}$ | 24.82                                   |
| $NO_2C_6H_4COOH$ (m) . . . . .           | $3.5 \times 10^{-4}$  | 5.91                                    |
| $NO_2C_6H_4COOH$ (p) . . . . .           | $3.9 \times 10^{-4}$  | 6.24                                    |
| $CH_3C_6H_4COOH$ (o) . . . . .           | $1.2 \times 10^{-4}$  | 3.46                                    |
| $CH_3C_6H_4COOH$ (m) . . . . .           | $5.1 \times 10^{-5}$  | 2.25                                    |
| $CH_3C_6H_4COOH$ (p) . . . . .           | $5.1 \times 10^{-5}$  | 2.25                                    |
| $C_6H_5CH_2COOH$ . . . . .               | $5.5 \times 10^{-5}$  | 2.34                                    |
| $NH_2C_6H_4COOH$ (o) . . . . .           | $1 \times 10^{-5}$    | 1.00                                    |
| $C_6H_4(COOH)_2$ (o) ( $K_1$ ) . . . . . | $1.21 \times 10^{-3}$ | 11.00                                   |

## DICARBOXYLIC ACIDS

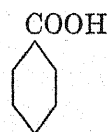
The three benzene dicarboxylic acids are the simplest and most important dibasic aromatic acids. They are known as *orthophthalic*, *metaphthalic*, and *paraphthalic* acids.



*o*-Phthalic acid  
(phthalic)



*m*-Phthalic acid  
(isophthalic)



*p*-Phthalic acid  
(terephthalic)

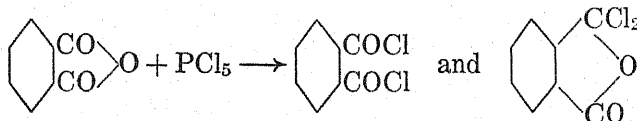
They may be prepared from the corresponding xylenes by boiling with dilute nitric acid or from the toluic acids by oxidation with alkaline permanganate solution. The ortho compound, ordinary phthalic acid, is manufactured commercially by oxidizing naphthalene with sulfuric acid. Mercury is used as a catalyst. The acid crystallizes in colorless prisms, melting between  $184^\circ$  and  $213^\circ$ . Failure to melt sharply at a definite temperature is due to its gradual loss of water, with the production of an anhydride. When either of the phthalic acids is

mixed with lime and heated gently, the first product formed is benzoic acid. At a higher temperature the benzoic acid is converted into benzene. Carbon dioxide is evolved in each step.

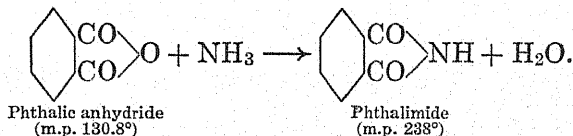
*Phthalic anhydride* is made by distilling phthalic acid or by passing a mixture of air and naphthalene vapor over hot vanadium oxide. It is used in the manufacture of phenolphthalein, the phthalein dyes, anthraquinone, and phthalimide.

Phthalic anhydride crystallizes in long, slender needles, melting at 130.8°. It takes up water very slowly, but dissolves rapidly in an alkaline solution, forming a salt of phthalic acid.

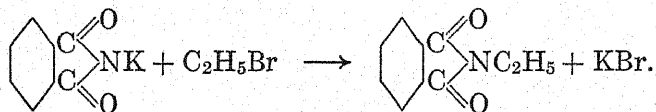
Phosphorus pentachloride acts upon phthalic anhydride, forming phthalyl chloride. This compound exists in two forms. One form, having a symmetrical structure, melts at 16°. The unsymmetrical chloride melts at 88°-89°.



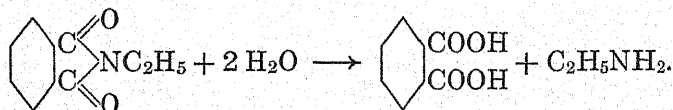
Phthalimide is made by passing ammonia over hot phthalic anhydride:



When potassium hydroxide is added to an alcoholic solution of phthalimide, potassium phthalimide is precipitated. The latter reacts readily with aliphatic halides:



On hydrolysis the alkyl derivative of phthalimide yields a primary amine:



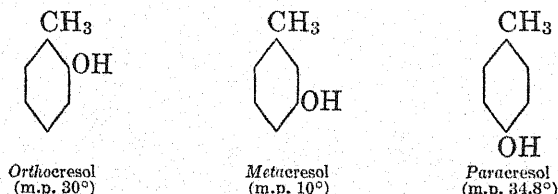
For other applications of this reaction (Gabriel's synthesis) see pages 140 and 418.



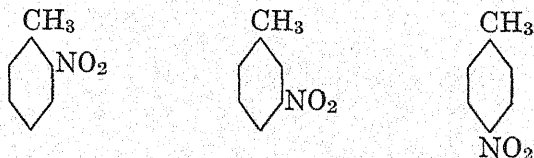
## ORIENTATION AND STERIC INFLUENCES OF SUBSTITUENTS

Any systematic procedure which enables us to assign definite positions to atoms or groups within a molecule constitutes a method of determining orientation. With reference to side chains or other substituents in cyclic compounds, two general methods of determining orientation have been developed.

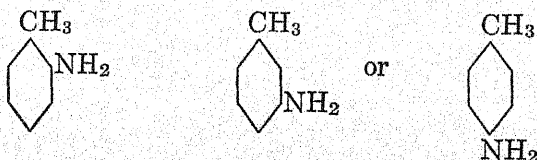
**The relative method.** A new derivative of benzene can usually be converted into a derivative of known structure by reactions which do not change the relative positions of the substituents, and thereby the structure of the new compound is revealed. For example, let us assume that the structures of the three cresols are known :



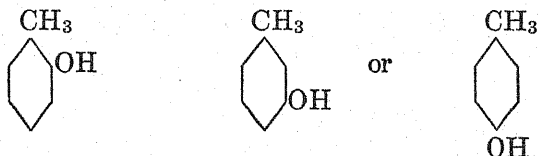
Three mononitro derivatives of toluene are known. One of them melts at 51.3°. Suppose the problem before us is that of deciding which of the following possible structures should be assigned to this particular compound :



By reducing the nitro compound with tin and hydrochloric acid the corresponding amino derivative is obtained :



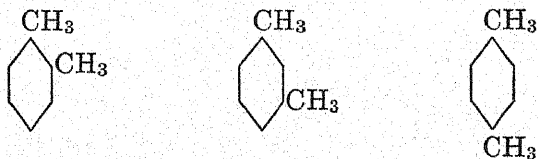
The amino group is readily replaced by hydroxyl through the diazo reaction, and the resulting phenol is



From the nitro compound melting at  $51.3^{\circ}$  we obtain a phenol (in this case a cresol) melting at  $34.8^{\circ}$ . Our compound is, therefore, *paranitrotoluene*. Similarly, a nitrotoluene melting at  $15.5^{\circ}$  yields a cresol melting at  $10^{\circ}$  and is therefore a *metanitro* compound, while a nitrotoluene melting at  $10.5^{\circ}$  yields a cresol which melts at  $30^{\circ}$ , and we assign to it the *ortho* structure. The *orthonitrotoluene*, on reduction, yields a toluidine which boils at  $200.7^{\circ}$ . *Metanitrotoluene*, when reduced, yields *metatoluidine*, boiling at  $203^{\circ}$ , and the *para* compound gives rise to crystalline solid toluidine, melting at  $43^{\circ}$  and boiling at  $200.5^{\circ}$ . From this point on, the toluidines and the nitro compounds, as well as the cresols, may serve as known structures, to which new compounds may be referred.

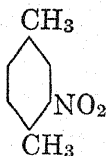
The relative method is based upon the assumption that a few structures for reference have been definitely established by other means. It is necessary, therefore, to determine the structures of a limited number of compounds without reference to known derivatives. The most successful plan for accomplishing this is Körner's absolute method of orientation.

The absolute method. There are three xylenes :

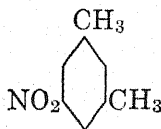
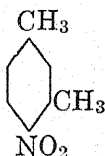
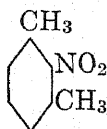


One of them melts at  $-53.6^{\circ}$ , one at  $-27.1^{\circ}$ , and the other at  $13.2^{\circ}$ . The corresponding boiling points are  $139^{\circ}$ ,  $144^{\circ}$ , and  $138^{\circ}$ . Which of the three formulas should be assigned to the compound that melts at  $-53.6^{\circ}$ , and which corresponds to each of the other sets of physical properties? On treatment with nitric acid, the xylene melting at  $-27.1^{\circ}$  yields two different mononitro derivatives. It is possible to obtain three isomeric

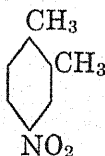
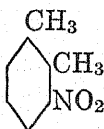
mononitroxylenes from the one that melts at  $-53.6^\circ$ , but only one mononitroxylene is formed from the compound melting at  $13.2^\circ$ . Now, *paraxylene* can form only one monosubstitution product, for the four hydrogen atoms remaining in the ring are similarly located in a symmetrical molecule. The nitro group must become attached to the ring, *ortho* to one methyl group and *meta* to the other:



From *metaxylene* three mononitro derivatives may be formed:



and from the *ortho* compound two and only two monosubstitution products can be prepared:



Hence the xylenes melting at  $-53.6^\circ$ ,  $-27.1^\circ$ , and  $13.2^\circ$  are *meta*, *ortho*, and *para* compounds respectively.

### DIRECTING INFLUENCES OF SUBSTITUENTS

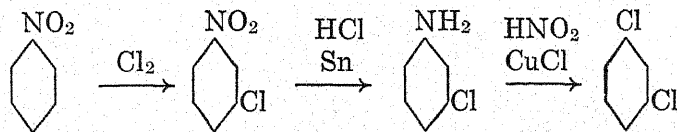
When a monosubstitution product of benzene is converted into a disubstitution product, there exists the possibility of forming either an *ortho*, a *meta*, or a *para* compound, or a mixture of these. The three derivatives are not formed in equal quantities. The product is almost exclusively the *meta* compound, or else it is a mixture of the *ortho* and *para* compounds. Whether the second substituent shall enter the *meta* position or shall be distributed between the *ortho* and *para* positions depends upon the group already present in the ring. Thus, for example, when chlorobenzene is nitrated, we obtain

chiefly *p*-chloronitrobenzene but also some of the *ortho* compound. If, on the other hand, we chlorinate nitrobenzene, we obtain, almost exclusively, *m*-chloronitrobenzene. The groups  $\text{NH}_2$ ,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{OH}$ ,  $\text{Cl}$ ,  $\text{Br}$ ,  $\text{I}$ ,  $\text{CH}_2\text{COOH}$ ,  $\text{SH}$ ,  $\text{CH}_2\text{Cl}$ ,  $\text{CH}_2\text{CN}$ , and  $\text{C}_6\text{H}_5$  are among those which, if already in the ring, direct the entering substituent to *ortho* and *para* positions. Among the groups that direct to the *meta* position are  $\text{NO}_2$ ,  $\text{SO}_3\text{H}$ ,  $\text{CN}$ ,  $\text{CHO}$ ,  $\text{COOH}$ , and  $\text{COOR}$ .

The groups  $\text{CCl}_3$  and  $\text{CF}_3$  direct chlorine and bromine to *ortho* and *para* positions, but nitration of benzotrichloride,  $\text{C}_6\text{H}_5\text{CCl}_3$ , or of benzotrifluoride occurs in the *meta* position. Other irregular nitration processes have been observed. In the presence of a large amount of concentrated sulfuric acid aniline and nitric acid yield *m*-nitroaniline.

The directing influence is never quantitative. Mixed products are always obtained, although in some cases the products formed belong almost exclusively to one type or the other. The ratios between *ortho*, *meta*, and *para* compounds change with any modification of the procedure. The ratios are not the same for a chlorination as for a nitration, and they are influenced by the solvent, the temperature, and other factors.

Indirect methods are used to synthesize derivatives having elements of the first group *meta* to each other, or elements of the second group in *ortho* or *para* positions. For instance, *m*-dichlorobenzene may be made by chlorinating nitrobenzene, then reducing the nitro group, diazotizing, and warming the diazonium salt with cuprous chloride:



The introduction of a third substituent into the ring brings into play the orienting influences of both groups already present. Suppose, for example, that we brominate sulfanilic acid,  $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{SO}_3\text{H}$ . Both groups direct the entering bromine atom to the same place, namely, *ortho* to the amino radical, but the bromination of *p*-chloroaniline,  $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{Cl}$ , involves the introduction of the entering bromine *meta* to either chlorine or the amino group, in opposition to the influence of a radical

of the first list. In this case the bromine enters the ring *ortho* to the amino group, indicating that the influence of the  $\text{NH}_2$  group is greater than that of chlorine. In *p*-aminophenol bromination occurs *ortho* to the hydroxyl group. Attempts have been made to list the principal radicals in the order of their power to determine the orientation of substituents in the benzene nucleus, but the place assigned to a group in such a series varies as determined by different types of reactions.\*

Many attempts have been made to reduce the empirical rules of substitution reactions to a definite system. Some of the more fruitful efforts in this direction may be summarized briefly.

**Crum-Brown and Gibson rule.**† If the radical already present forms a compound with hydrogen which can be readily and directly oxidized to a corresponding hydroxyl derivative, the entering substituent will take the *meta* position; otherwise it will enter the *ortho-para* positions. Thus,  $\text{CHO}$  forms the compound  $\text{H} \cdot \text{CHO}$ , which is oxidized to  $\text{H} \cdot \text{COOH}$  without the formation of an intermediate product, but  $\text{NH}_2$ , by addition of hydrogen, yields ammonia,  $\text{H}\text{NH}_2$ , which cannot be converted in one step into  $\text{NH}_2\text{OH}$ . The former, therefore, governs the *meta* and the latter the *ortho-para* positions.

**Flürscheim's theory.** Adopting Werner's theory of valence, Flürscheim‡ assumes that the affinity of any free atom is evenly distributed over its surface, but when this affinity or part of it is used in holding other atoms, it may become concentrated in small areas, the distribution being dependent upon the environment and the nature of the atoms attached. An element or group that has a strong affinity for carbon, such as  $\text{Cl}$ ,  $\text{OH}$ , or  $\text{NH}_2$ , when attached to carbon in the benzene ring pulls toward itself a large share of the total disposable surface attraction. This weakens the union between the carbon atom involved and the two *ortho* carbon atoms, leaving on the *ortho* carbon atoms a surplus of affinity for the attachment of the entering substituent. A nitro group, on the other hand, is supposed to be loosely bound to carbon, using less of the disposable affinity of the carbon atom. The union between this carbon atom and an adjacent atom in the ring becomes firmer, the

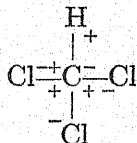
\* For a tabulation of experimental results see A. F. Holleman, *Die direkte Einführung von Substituenten in den Benzolkern*.

† Crum-Brown and Gibson, *Trans. Chem. Soc.*, 61, 867 (1892).

‡ Flürscheim, *J. prakt. Chem.* (2), 179, 497 (1905).

major portions of their affinities being called into play in effecting the linkage between them. The *ortho* carbon atoms, therefore, have less residual affinity than is possessed by those in the *meta* positions. Part of the excess of free affinity possessed by each *meta* carbon atom is used in strengthening the *meta-para* union. The residual valence of the *para* carbon is thus decreased and its activity is reduced. The surplus free affinity resides upon either the *meta* or the *ortho* and *para* carbon atoms, as determined by the type of union that exists between the ring and the substituent already present.

The electron theory. In the early days of the development of the electron theory it was assumed that chemical union was due to the complete passage of an electron from one atom to another rather than the sharing of electrons between the atoms involved. In harmony with this view each atom in a compound was represented as having an integral number of unit positive charges corresponding to the number of electrons it had lost or an integral number of negative charges corresponding to the number of electrons gained. Thus the formula of chloroform,  $\text{CHCl}_3$ , was written:



The signs indicated that the carbon atom had acquired an electron from hydrogen and yielded an electron to each of the three chlorine atoms.

The transfer of electrons between carbon atoms was represented as taking place in the direction that would leave one atom as fully oxidized (positive) as possible and the adjacent carbon atom as completely reduced as possible. There is considerable evidence in support of the view that alternating polarities exist in carbon chains and rings.

The idea of a complete transfer of electrons from one atom to another, in compounds that do not ionize, has been abandoned. Chemists generally agree, now, that the electrons involved in a chemical bond are shared by the positive kernels of the two atoms concerned. When the union is between different kinds of atoms it is assumed that the electrons are drawn nearer to the electronegative element, and Stieglitz has suggested

that we may still use, with advantage, the plus and minus signs to indicate even a slight displacement of electrons from the central position between any two atoms in a compound. Without specifying the extent of the electronic displacement we may consider hydrogen positive with respect to oxygen in the hydroxyl group, and this difference in character may be indicated by a plus sign over the symbol for hydrogen and a minus sign over the symbol for oxygen. Electrochemical differences between other atoms may be indicated in the same way.

Assuming that a group substituted for hydrogen in the benzene ring induces alternate positive and negative charges on the atoms in the ring, we should have the following orientations of charges in phenol and nitrobenzene:

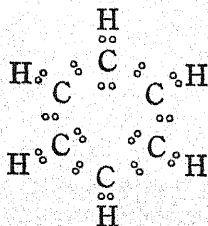


If, now, we make the further assumption that substitution occurs on the relatively negative carbon atoms, we have an explanation of most of the reactions of benzene.

Latimer and Porter have written a formula for benzene based upon the following considerations:

1. There are thirty valence electrons in the benzene molecule — an average of five electrons per carbon atom.
2. In stable molecules atomic nuclei are not associated with odd numbers of electrons. There is a tendency for each carbon atom to complete its octet, but when this is impossible, there will be a distribution of such a character as to leave an even number of electrons for each atom.
3. The benzene molecule is symmetrical.

In harmony with these facts the distribution of the electrons is assumed to be approximately as follows:



Each alternate carbon atom has a complete octet; each of the others has a sextet. The lone pairs of electrons may shift from one carbon atom to the next, the result being analogous to the effects of shifting the alternate double bonds in the Kekulé formula. When an atom carrying a negative charge is substituted for hydrogen, the carbon to which it is attached retains only six electrons, the *para* and the two *ortho* carbon atoms each having eight. When the atom substituted for hydrogen in the ring has a positive residual charge, the nuclear carbon to which it is attached will hold a complete octet.

Thus for bromobenzene and nitrobenzene we have



With the formation of a monosubstitution product the possibility of an electronic rearrangement disappears. In the substituted ring the six and eight positions are relatively fixed. The eight positions are *meta* to a nitro group and *ortho-para* to bromine, and this orientation of electrons determines the position to be taken by the next entering group. It is obvious that this formula may be written in the form\* proposed by Stieglitz. It is only necessary to indicate by plus signs the carbon atoms sharing six electrons and by minus signs those having complete octets.

By estimating the magnitude of the charge on the atom attached to the ring, it is possible to draw a fairly sharp line between the groups that direct to the *meta* position and those that cause *ortho-para* orientation.\*

Ingold and his associates have accounted for the orientation of substituents in the benzene ring by an extension of the Flürscheim theory. A critical discussion of the system is beyond the scope of this book. The papers listed below are recommended for study:

J. Allan and R. Robinson, *J. Chem. Soc.*, 1926, 376.

Holmes and Ingold, *J. Chem. Soc.*, 1926, 1305, 1684.

Ingold, *Rec. trav. chim. Pays-Bas*, 48, 797 (1929).

\* For a discussion of this system see Latimer and Porter, *J. Am. Chem. Soc.*, 52, 206 (1930).



## ENHANCED ACTIVITY

Bromine acts slowly upon benzene, forming bromobenzene and hydrobromic acid. A catalyst is required to accelerate the reaction in order to make it a practical method of preparation. If we introduce a hydroxyl group or an amino group into the ring, then the *ortho* and *para* hydrogen atoms of the resulting phenol or amine are at the same time rendered more reactive. Even a dilute solution of bromine in water immediately precipitates tribromophenol and tribromoaniline from solutions of phenol and aniline. Iodine replaces the hydrogen atoms *ortho* to the hydroxyl group in tyrosine when iodine is added to an aqueous alkaline solution of this amino acid. The reaction occurs at 0° C. and the di-iodo derivative separates in crystalline form when the excess alkali is neutralized by acetic acid. Phenylalanine fails to react with an alkaline hypoiodite solution in this way.

In the aliphatic series similar effects have been observed. It will be recalled that the carbonyl group enhances the activity of hydrogen on the  $\alpha$ -carbon atom. This effect is noticed in the aldol condensation, in the reactions of acetoacetic ester and malonic ester, in Perkin's synthesis, and in the chlorination of saturated acid chlorides. The capacity of a carbonyl group to accelerate the hydrolysis of an adjacent carbon-oxygen bond is revealed by the fact that ethers are hydrolyzed with great difficulty, whereas esters and acid anhydrides are readily hydrolyzed.

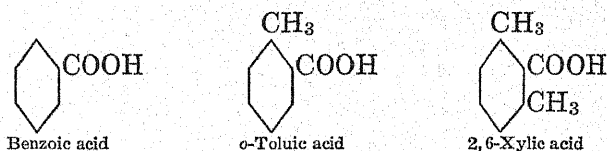
The chlorine in chlorobenzene is very firmly held; but chlorine in trinitrochlorobenzene is extremely reactive. A commercial method for making picric acid is based upon this increased activity of the halogen atom. Chlorobenzene is nitrated and the halogen is subsequently replaced by hydroxyl by merely boiling with water. The *para* hydrogen in an amine or phenol is much more active than hydrogen in unsubstituted benzene. Upon this enhanced activity depends the formation of the azo dyes, triphenylmethane dyes, and phthaleins.

## DIMINISHED ACTIVITY

When carbon tetrachloride is warmed with benzene in the presence of aluminum chloride or with bromobenzene and sodium, three of the chlorine atoms are replaced by phenyl radicals, but the fourth chlorine atom is not removed by

these reagents. The ease with which triphenylchloromethane,  $(\text{C}_6\text{H}_5)_3\text{CCl}$ , triphenylmethane,  $(\text{C}_6\text{H}_5)_3\text{CH}$ , and triphenylcarbinol,  $(\text{C}_6\text{H}_5)_3\text{COH}$ , are formed and the failure to secure tetraphenylmethane,  $(\text{C}_6\text{H}_5)_4\text{C}$ , under similar conditions, led Victor Meyer to the conclusion that there was not room enough for the direct attachment of four phenyl radicals to a single carbon atom. He believed that three such groups and one smaller radical could be packed into the space around the methane carbon without forcing any one of them out to a point beyond the central atom's range of attraction, but the fourth large group was excluded for lack of room. Meyer referred to this phenomenon as steric hindrance.

The diminished activity of an atom or group between two side chains on the benzene ring was explained also as due to steric hindrance. Aniline and toluidine form addition products with alkyl halides, but if side chains be introduced in both positions, *ortho* to the amino group, addition of an alkyl halide either fails to occur or takes place very slowly. Similarly, benzoic acid, with an alcohol, readily forms an ester; *o*-toluic acid reacts more slowly and 2,6-xylic acid can hardly be esterified at all by the usual direct method.

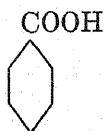


It has been shown, however, that the failure to form such compounds as tetraphenylmethane and esters of di-*ortho* substituted acids is not due to lack of room for an entering group. By indirect means Gomberg made tetraphenylmethane, and instead of being an unstable compound, as would be expected if the phenyl groups were crowding each other away from the central carbon atom, it proved to be a very stable substance, melting at  $285^\circ$  and distilling unchanged at  $431^\circ$ . A di-*ortho* substituted acid which fails to form an ester when treated with alcohol may be esterified by the action of its silver salt on ethyl iodide, and, when formed, the ester is not readily hydrolyzed. Steric hindrance, therefore, is not due to insufficient space for the attachment of a large group. It is a retarding of the rate of change due in some degree, perhaps, to obstruction afforded

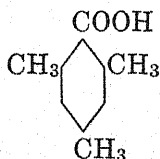
by the surrounding groups, but due primarily to chemical influences of the *ortho* substituents, comparable to the accelerating effects of the various groups discussed under Enhanced Activity.

The interference or hindrance varies with the chemical nature of the groups occupying the *ortho* positions, and in its effect upon the rate of ester formation from aromatic acids it increases in the following order: chlorine, alkyl radical, hydroxyl, bromine, iodine, nitro group.

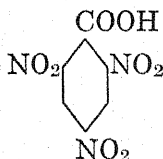
Benzoic, trimethylbenzoic, and trinitrobenzoic acids were warmed with methyl alcohol and hydrogen chloride for three hours. The per cent of acid esterified is indicated under each formula.



Benzoic acid,  
90% esterified

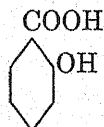


Trimethylbenzoic acid,  
48% esterified

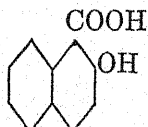


Trinitrobenzoic acid,  
6% esterified

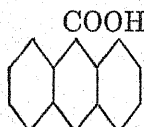
Results of another esterification experiment are given below. The acids were mixed with methyl alcohol and hydrogen chloride, and held at a temperature of 20° for eight hours:



Salicylic acid,  
34% esterified

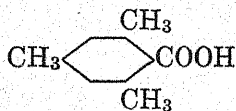


$\beta$ -Hydroxynaphthoic acid,  
3% esterified

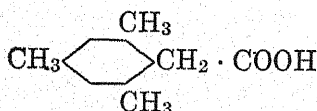


$\alpha$ -Anthracene carboxylic acid,  
no ester formed

*Ortho* substituents do not retard esterification if the carboxyl group is remote from the ring. It is difficult to esterify trimethylbenzoic acid, but trimethylphenylacetic acid reacts with alcohol as rapidly as does benzoic acid:



Trimethylbenzoic acid,  
slowly esterified



Trimethylphenylacetic acid,  
rapidly esterified

It is possible to account for this effect on the purely physical basis of steric hindrance — the carboxyl group in trimethyl-

phenylacetic acid being beyond the protective influence of the methyl radicals. It is equally easy, in this case, to apply the chemical theory, for removal of the carboxyl group from the ring would virtually nullify, or it might even reverse, the chemical influence that the *ortho* substituents exert upon it. If steric hindrance were due to physical rather than to chemical influences, then long side chains should be much more effective than short ones. As a matter of fact, there is little, if any, difference in the potency of aliphatic hydrocarbon radicals, and no alkyl radical, however long, produces a hindering influence comparable to that of the nitro group.\* Hufferd and Noyes† have measured the rates of esterification of xylic acids,  $(\text{CH}_3)_2\text{C}_6\text{H}_3\text{COOH}$ , and have obtained results which they believe support Meyer's theory that *ortho* substituents actually shield the carboxyl group from reagents that would otherwise reach it.

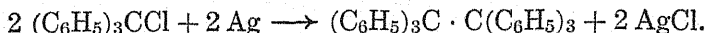
\* For a summary of the literature relating to steric hindrance, see A. W. Stewart's "Stereochemistry."

† Hufferd and Noyes, *J. Am. Chem. Soc.*, **43**, 925 (1921).

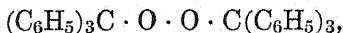
See also Adams and Yuan, *Chem. Rev.*, **12**, 261-338 (1933).

## FREE RADICALS

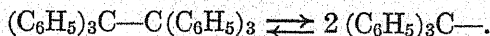
In 1900, Gomberg\* prepared hexaphenylethane by the action of finely divided metallic zinc or silver on a solution of triphenylchloromethane:



Unlike an ordinary saturated hydrocarbon, this compound dissolved in benzene or ether, with the development of color (yellow). The color was discharged when the solution was exposed to the air and a crystalline peroxide,



precipitated. The hydrocarbon absorbed bromine and iodine, with the formation of triphenylmethyl halides,  $(\text{C}_6\text{H}_5)_3\text{CBr}$  and  $(\text{C}_6\text{H}_5)_3\text{CI}$ . It therefore behaved like a highly unsaturated compound, but, unlike compounds having multiple bonds, it formed halogen addition products with only one halogen atom in each molecule. This unusual behavior of the hydrocarbon led Gomberg to conclude that the solution contained free half-molecules of hexaphenylethane, namely, triphenylmethyl,  $(\text{C}_6\text{H}_5)_3\text{C}\cdot$ . Further study confirmed the opinion that in nonpolar as well as in ionizing solvents hexaphenylethane dissociates, establishing an equilibrium between the free radicals and the undissociated molecules:

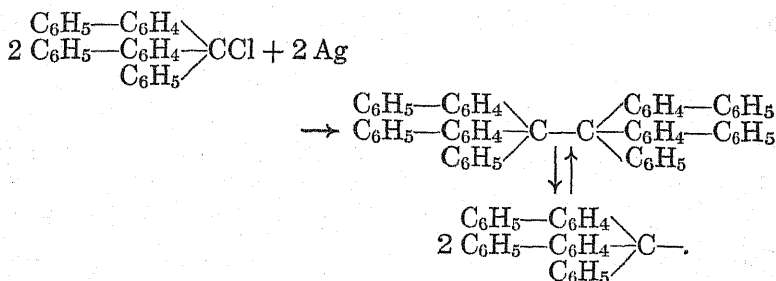


The molecular weight of the hydrocarbon, determined by the cryoscopic method, was found to be 480 in benzene and 407 in naphthalene. The calculated value for the undissociated molecule is 486.

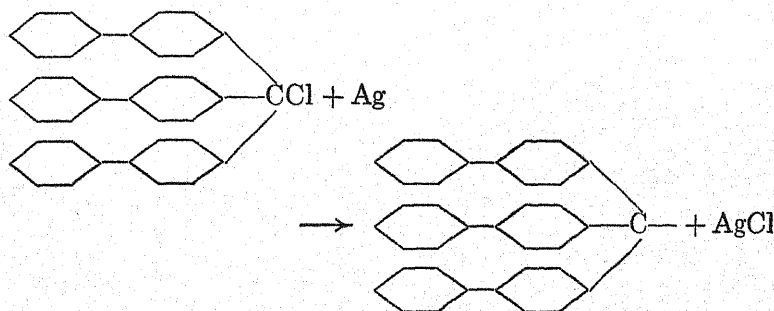
With more complex groups attached to the tertiary carbon, much larger yields of free radicals are obtained. Thus, for example, phenyldibiphenylchloromethane, when dissolved in

\* Gomberg, *J. Am. Chem. Soc.*, **22**, 757 (1900). Gomberg, *Ber.*, **33**, 3150 (1900). Gomberg and Bachmann, *J. Am. Chem. Soc.*, **52**, 2455 (1930).

benzene and treated with molecular silver, yields a product which is 80 per cent dissociated :



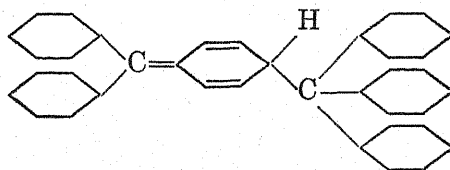
Tribiphenylmethyl chloride with silver in dry benzene yields the free radical only. That is to say, hexabiphenylethane in dilute benzene solution is 100 per cent dissociated into tribiphenylmethyl,  $(\text{C}_6\text{H}_5 \cdot \text{C}_6\text{H}_4)_3\text{C}-$ .



These radicals, as they exist in solution in benzene, are not the ions of an electrolyte. The benzene solution is not a conductor of electricity. In liquid sulfur dioxide and in other ionizing solvents they are good conductors of electricity, the dissociation being of such character that the pair of electrons constituting the valence bond between the ethane carbon atoms are both held by the same radical (the negative ion). In non-polar solvents the dissociation results in the formation of two identical electrically neutral radicals.

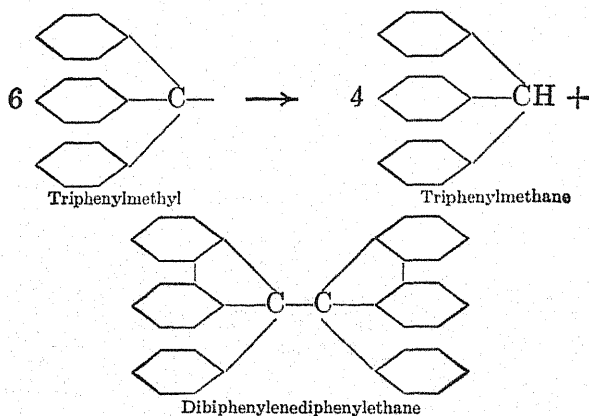
The preparation of free radicals involves a fine technique. The radicals combine rapidly not only with air, water, and the halogens, but from complex addition products with many types of so-called saturated organic compounds such as phenols, alcohols, esters, and some ethers. They are sensitive to light

and heat, undergoing various types of rearrangement or decomposition. Triphenylmethyl, for example, is converted by hydrogen ions into benzhydryltetraphenylmethane,

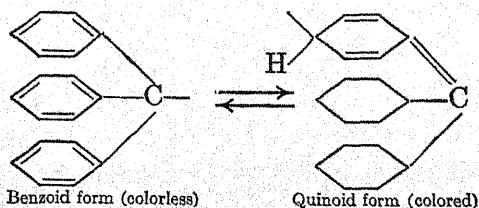


Benzhydryltetraphenylmethane

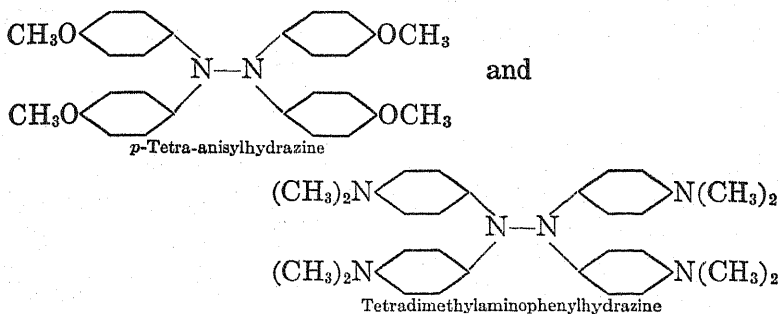
It yields two saturated hydrocarbons under the influence of light:



All these free radicals yield colored solutions. One or two representatives of the group are colorless at low temperatures, but color develops when they are warmed. Most of them are colorless in the solid state. Gomberg attributes the color in every instance to the formation of the quinoid structure in one of the rings, assuming an equilibrium of the following type:

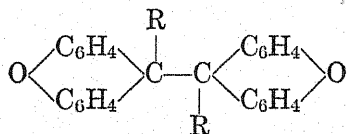


Evidence of the existence of divalent nitrogen has been found in the behavior of substituted tetraphenylhydrazines, such as

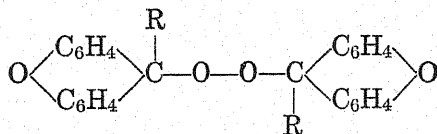


These compounds form addition products and in solution have molecular weights below the calculated values for undissociated molecules.\*

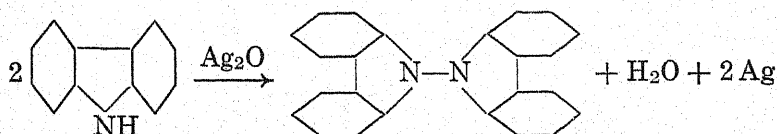
Conant and his colleagues have prepared many derivatives of dixanthyl corresponding to the general formula



These compounds are soluble in bromobenzene. In this solvent they dissociate and, if air is not excluded, they yield crystalline peroxides of the following type :†



Branch and Smith ‡ oxidized carbazole by means of moist silver oxide to secure dicarbazyl :



\* Wieland and Gambarjan, *Ber.*, **39**, 1499 (1906). Hantzsch, *Ber.*, **39**, 2478 (1906).

† James B. Conant and Mildred W. Evans, *J. Am. Chem. Soc.*, **51**, 1925 (1929).

‡ Branch and Smith, *J. Am. Chem. Soc.*, **42**, 2405 (1920).



It was reasonable to assume that this hydrazine derivative might dissociate to a greater extent than did Wieland's compounds. The reaction did not proceed in exact accordance with the above equation. An unsaturated nitrogen compound was formed, but its structure was not definitely established.

A substituted ammonium radical was obtained in the form of an amalgam by McCoy and West.\* Tetramethylammonium chloride was decomposed by electrolysis in the presence of a mercury cathode. The radical  $(\text{CH}_3)_4\text{N}$ , acting like a free metal, formed an amalgam with the mercury.

Attempts have been made to obtain compounds of univalent oxygen,† bivalent arsenic,‡ trivalent silicon,§ and radicals of other elements, but most of these attempts have been unsuccessful.

Hexaphenylsilicoethane,  $(\text{C}_6\text{H}_5)_3\text{Si} \cdot \text{Si}(\text{C}_6\text{H}_5)_3$ , displays none of the properties of hexaphenylethane. It is a very stable compound that melts above  $300^\circ$ , has no color in any solvent, and forms no peroxide.

A solution of *bis*-lead triphenyl,  $(\text{C}_6\text{H}_5)_3\text{Pb} \cdot \text{Pb}(\text{C}_6\text{H}_5)_3$ , acquires a weak color at high temperatures but forms no peroxide and gives no other evidence of dissociation.

\* H. N. McCoy and F. L. West, *J. Phys. Chem.*, **16**, 261 (1912).

† Pummerer and Frankfurter, *Ber.*, **47**, 1472 (1914). Porter and Thurber, *J. Am. Chem. Soc.*, **43**, 1194 (1921). Goldschmidt, Schulz, and Bernard, *Ann.*, **478**, 1 (1930).

‡ Porter and Borgstrom, *J. Am. Chem. Soc.*, **41**, 2048 (1919).

§ Schlenk, Renning, and Racky, *Ber.*, **44**, 1178 (1911).

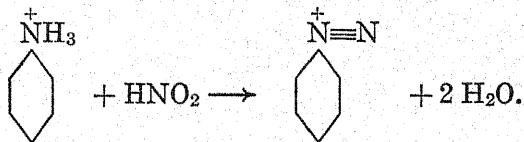
## DYES

A dye is a colored compound which is capable, either directly or with the aid of a mordant, of imparting a permanent color to textile fibers. The practical dyer lists such substances in two principal groups: (1) those that dye fibers directly (substantive dyes), and (2) those that require mordants (adjective dyes).

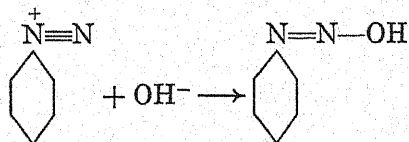
The mordants commonly employed are aluminum, iron, chromium and tin salts, tannic acid, calcium phosphate, albumin, and finely divided silica. The choice of mordant is determined by the character of the dye.

### AZO DYES

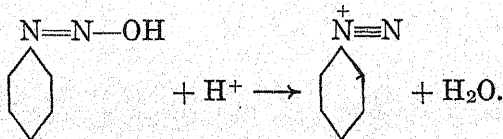
Any primary aromatic amine may be diazotized by nitrous acid (see page 224). The reaction is usually carried out by adding sodium nitrite to an acid solution of an amine salt. A diazonium salt is thus formed.



When the excess of acid in the solution is neutralized by the addition of a base, the diazonium salt is converted into a diazo compound.

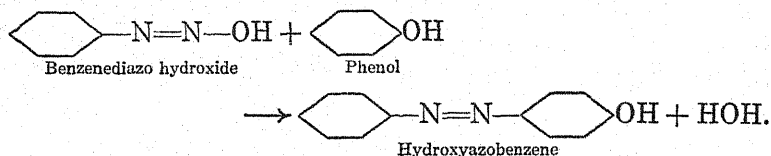


The reaction is reversible. Strong acids regenerate diazonium salts from the diazo compounds.



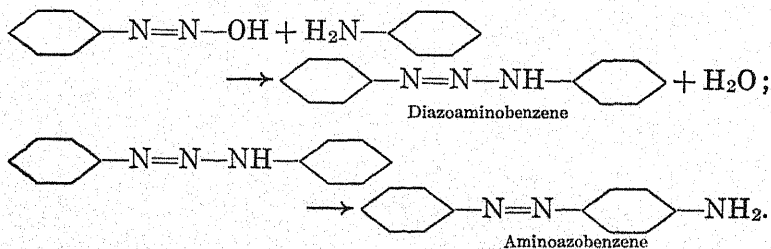
The diazo compound can exist in the presence of weak acids as well as in the presence of bases. A hydrochloric acid solution of benzenediazonium chloride is converted into benzenediazo hydroxide by the addition of sodium acetate.

Diazo compounds and diazonium salts combine with phenols and with aromatic amines forming azo dyes.



It is the hydrogen atom *para* to the hydroxyl group in the phenol that is replaced. If the *para* position is occupied by any element or group other than hydrogen, coupling occurs in an *ortho* position; and if the *para* and both *ortho* positions are so occupied, then coupling usually fails to occur and no dye is formed. In rare instances a *para* substituent is replaced by the diazo group. The same rules apply to the union of a diazo compound with a tertiary amine such as dimethylaniline.

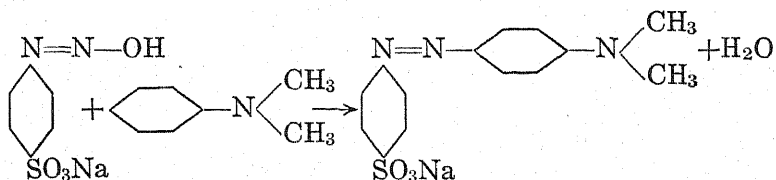
When a primary or secondary amine is coupled with a diazo compound, an intermediate product, known as a diazoamino compound, is usually formed by replacement of hydrogen attached to nitrogen. Thus diazotized aniline combines with unchanged aniline, yielding diazoaminobenzene in the form of golden-yellow plates. When this is warmed with hydrochloric acid or aniline hydrochloride, a rearrangement occurs and the hydrochloride of aminoazobenzene is precipitated in the form of steel-blue needles.



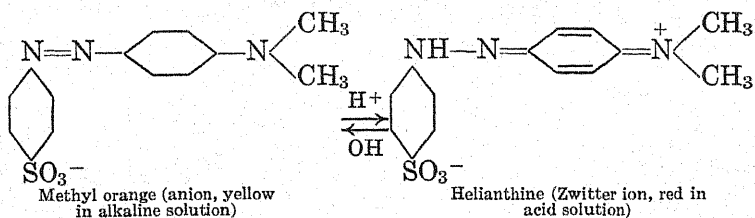
In any case where a diazoamino compound is formed, this rearrangement may be induced by warming a solution of the compound with an acid or with an excess of the corresponding

amine hydrochloride. It is an application of the Hofmann reaction (pages 214 and 447).

*Helianthine*. Dimethylaminoazobenzenesulfonic acid, or helianthine, is prepared by mixing cold aqueous solutions containing equivalent quantities of diazotized sulfanilic acid and dimethylaniline hydrochloride. The sodium salt of the compound is the yellow dye known as methyl orange. It is used as an indicator in the titration of acids and bases. Its sensitiveness to changes in the concentrations of hydrogen and hydroxide ions — the property that makes it a valuable indicator — renders it useless as a dye. The preparation of methyl orange is represented by the following equation:



In acid solution methyl orange is converted into the red dye helianthine. In alkaline solution the process is reversed. The color change is due to a structural rearrangement in the molecule. These compounds are electrolytes, and the colored ions are represented by the following formulas:



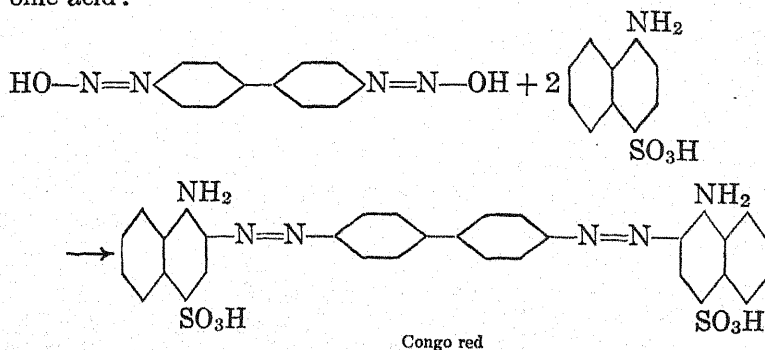
An ion bearing a positive charge in one position and a negative charge at another point is called a *Zwitter ion*. Helianthine displays this type of ionization. The reversible color change takes place when the hydrogen ion concentration of the solution is varied between values corresponding to  $p\text{H} = 3.1$  and  $p\text{H} = 4.4$ . The  $p\text{H}$  of a solution was defined by means of an equation in the chapter on monobasic acids.

Similar changes in structure are produced by acids and bases on methyl red. Methyl red is made by adding dimethylaniline

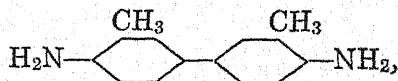
hydrochloride to a solution of diazotized anthranilic acid and sodium acetate. The dye is red in acid solution and yellow in alkaline solution. The change in color occurs within the range of  $pH=4$  and  $pH=6$ .

Tetrazo compounds, formed from benzidine with the naphthols, naphthylamines, and related bodies, constitute the Congo group of dyes. The latter possess the valuable property of dyeing cotton without mordants.

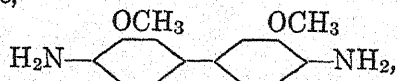
Congo red is formed from diazotized benzidine and naphthionic acid:



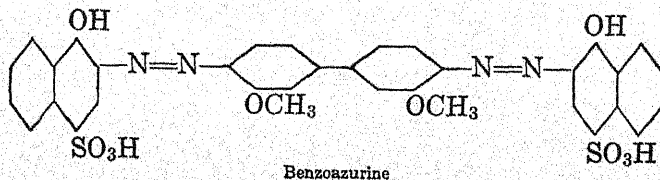
The substitution of tolidine,



or of dianisidine,



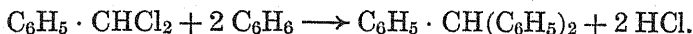
for benzidine shifts the color of the dye toward the violet end of the spectrum. Red predominates in all dyes derived from benzidine by coupling with naphthylamines. The corresponding naphthol derivatives display bluer shades. Tetrazotized dianisidine combines with  $\alpha$ -naphtholsulfonic acid to produce a pure blue dye called benzoazurine.



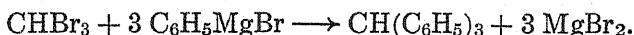
## TRIPHENYLMETHANE DYES

Triphenylmethane,  $(\text{C}_6\text{H}_5)_3\text{CH}$ , crystallizes in colorless prisms, melting at  $93^\circ$ , and boiling without decomposition at  $359^\circ$ . It is prepared by the following methods:

1. From benzal chloride and benzene in the presence of aluminum chloride:



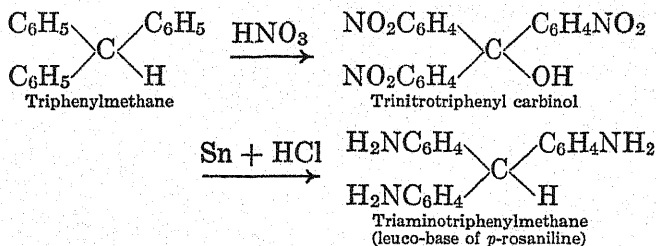
2. From chloroform or bromoform and phenyl magnesium bromide:



3. From benzaldehyde and benzene by warming the mixture with zinc chloride:



Many beautiful and valuable dyes are derived from this compound. The commercial methods employed in the preparation of these dyes do not involve the synthesis of triphenylmethane, but their relationship to this hydrocarbon has been traced by direct synthesis, as indicated in the following examples:

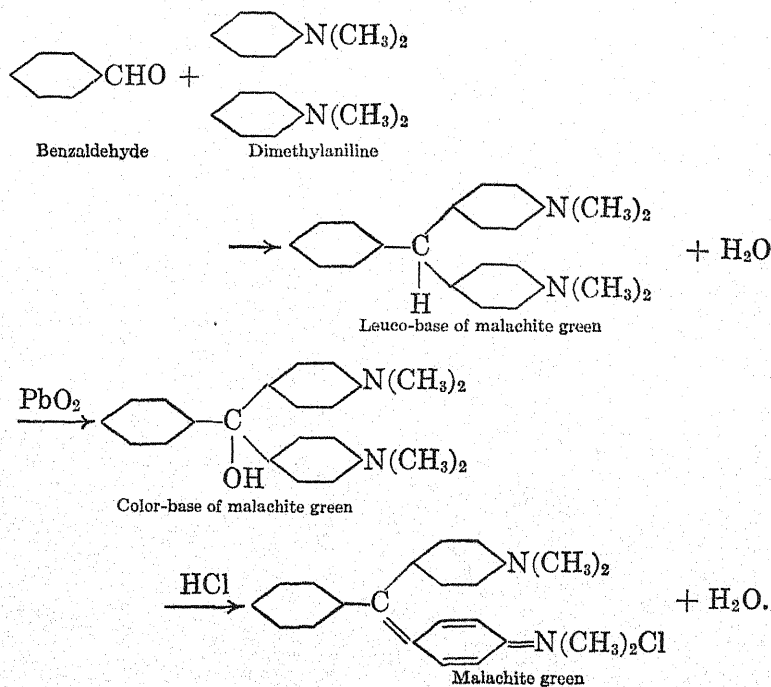


Beginning with the leuco-base of the dye, the parent substance, triphenylmethane, may be obtained through the diazo reaction.

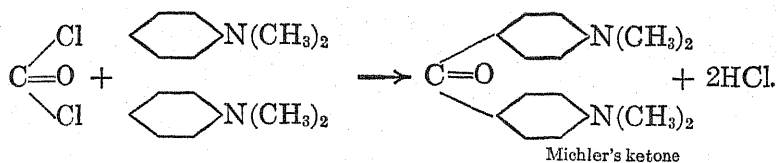
The leuco-base of a triphenylmethane dye is colorless. Mild oxidizing agents, such as nitrobenzene and lead dioxide, convert the leuco-base into a carbinol, called a color-base, which also is colorless. Dyes are derived from the color-base by the action of acids. The reaction, which is discussed later, consists of the addition of the acid to an amino group and subsequent elimination of water, with the establishment of a quinoid structure in one of the benzene rings.

The time required to complete the change in structure can be varied between a few seconds and several hours by control of the hydrogen ion concentration and the temperature. The process is reversible. Hydroxide ion reconverts the dye to the colorless color-base, water being taken up by the dye in alkaline solution, and simultaneously the quinoid ring goes back to the benzoid form.

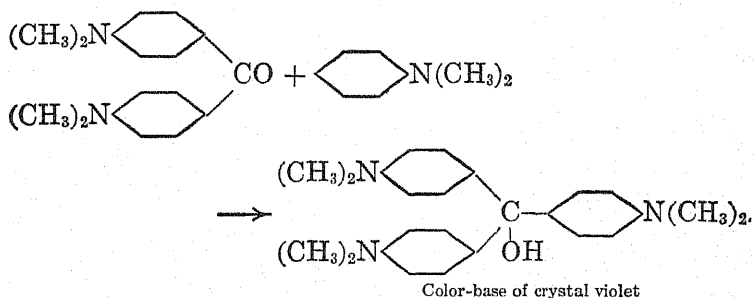
*Malachite green.* The leuco-base of tetramethyldiaminotriphenylmethane, or malachite green, is formed by the action of zinc chloride on a mixture of benzaldehyde and dimethylaniline. The leuco-base is oxidized to the color-base by lead dioxide and hydrochloric acid. The dye is obtained in the same reaction owing to the presence of hydrogen ions which bring about the dehydration and change of structure.



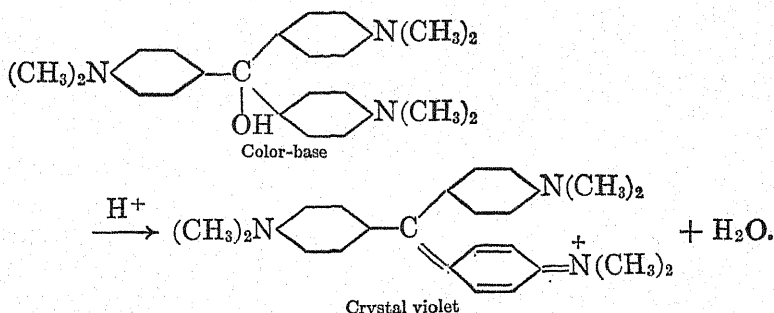
*Crystal violet.* Phosgene gas is absorbed by dimethylaniline, with the formation of tetramethyldiaminobenzophenone. Hydrogen chloride produced at the same time combines with the excess of dimethylaniline and with the ketone:



When warmed with phosphorus oxychloride a mixture of tetramethyldiaminobenzophenone (Michler's ketone) and dimethylaniline yields the color-base of crystal violet:



The carbinol, or color-base, is converted into the dye, hexamethyltriaminotriphenylmethane, by treatment with an acid:

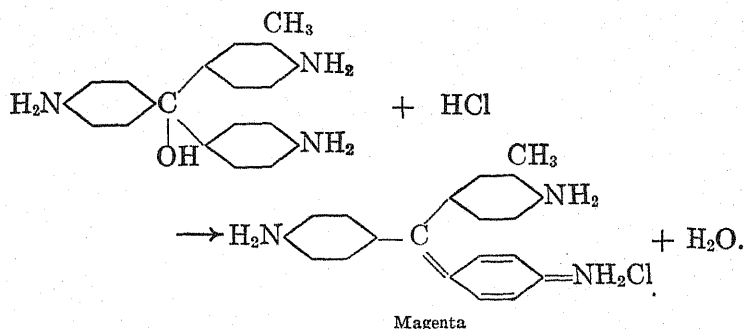


Like malachite green and other members of this class, crystal violet dyes silk and wool directly, but cotton is dyed only with the aid of a mordant such as tannic acid.

*Methyl violet* differs from crystal violet only in having one methyl group less in the molecule. It is pentamethyltriaminotriphenylmethane. The crystals have a bronze luster. The dye is produced from dimethylaniline by oxidation with cupric chloride, the methane carbon being derived from one of the methyl groups of the amine.

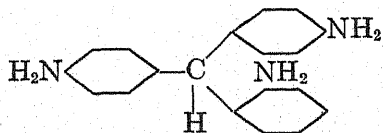




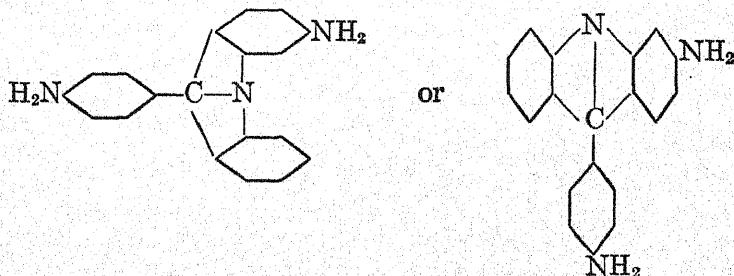


Many other dyes of this type have been made by oxidizing various mixtures of aromatic amines.

*Chrysaniline*, a yellow dye, is formed in small quantities as a by-product in the manufacture of pararosaniline. Its production is due to part of the aniline molecules condensing with toluidine through loss of hydrogen *ortho* to the amino group. The leuco-base of chrysaniline has the formula

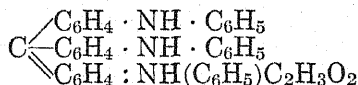


When this compound is oxidized by means of lead dioxide, the hydrogen on the central carbon atom is removed in the formation of water. At the same time water is formed by removal of hydrogen from the *ortho* amino group and from an *ortho* position in one of the other aniline residues. Two rings are thereby linked together through nitrogen as well as through the methane carbon. The resulting structure is



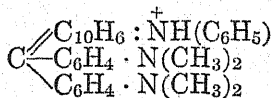
It is a typical representative of the acridine group of dyes.

The colors of the basic triphenylmethane dyes range from yellow to violet, and seem to be determined primarily by the character and number of groups substituted for hydrogen in the amino groups. Yellow, red, green, and violet representatives of the class have been mentioned. A blue dye is obtained by heating pararosaniline with an excess of aniline in acetic acid. The product formed, known as rosaniline-blue, has the following structure:

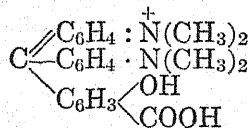


Only three phenyl groups can be substituted for amino hydrogen, one in each amino group. The corresponding compound with a phenyl group in only one of the amino groups is violet, and the diphenyl derivative is bluish violet.

Dyes of similar structure, having one or more of the phenyl groups of triphenylmethane replaced by naphthalene and anthracene radicals, have been prepared also. Victoria blue, for example, is made by treating tetramethyldiaminobenzophenone (Michler's ketone) with phenyl- $\alpha$ -naphthylamine; and chrom violet is made in a similar way from tetramethyldiaminobenzhydrol and salicylic acid.

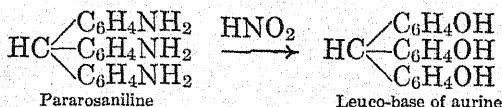


Victoria blue



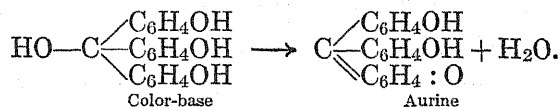
Chrom violet

The amino derivatives of triphenylmethane are basic dyes. The corresponding hydroxy compounds are acidic. The acidic dyes are less important than the basic dyes; for, as a rule, they fail to impart fast colors to textile fibers. *Aurine* and *rosolic acid*, typical members of the group, are obtained from pararosaniline and rosaniline, respectively, by the diazo reaction:



The dye is formed by oxidizing the leuco-base. An intermediate carbinol or color-base is undoubtedly produced, but it

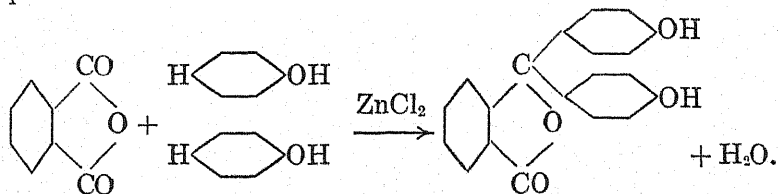
is unstable and has not been isolated. It loses water at once, with the establishment of a quinoid structure:



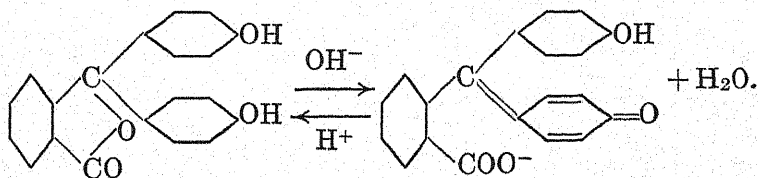
The color-bases of the monohydroxy and dihydroxy triphenylmethane derivatives are fairly stable and are known in the free state. The acidic dyes are colored in alkaline solution and colorless in acid solution.

### THE PHTHALEINS

*Phenolphthalein.* Phenol condenses with phthalic anhydride when heated with anhydrous zinc chloride, forming phenolphthalein:

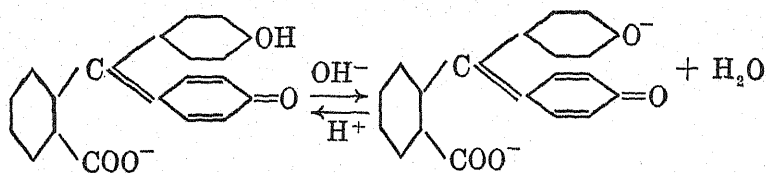


The compound is colorless in neutral and in acid solutions and red in alkaline solutions. It is used extensively as an indicator, for the color change is almost instantaneous and it occurs within a very narrow range of hydrogen and hydroxide ion concentrations, near the true neutral point. A base acts upon phenolphthalein, forming a salt, eliminating a molecule of water, and thereby establishing a quinoid structure. An acid reverses the process:



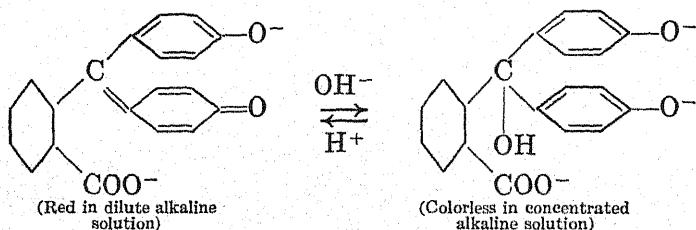
The colored form of phenolphthalein is produced by the addition of one more equivalent of base, which reacts with the remaining hydroxyl group.

This also is a reversible process :



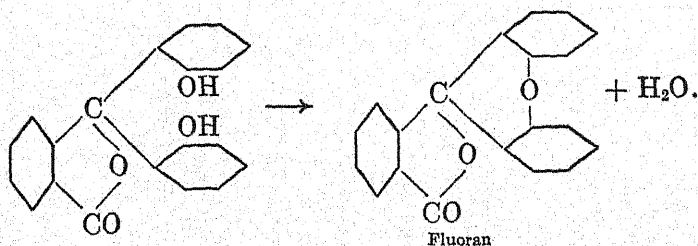
The salts ionize and they are quite soluble, but the acid, assuming the anhydride form, is un-ionized and only slightly soluble in water.

In the presence of a large excess of a base the red color of phenolphthalein gradually fades until the solution becomes colorless. The mechanism of this change is indicated by the following equation :



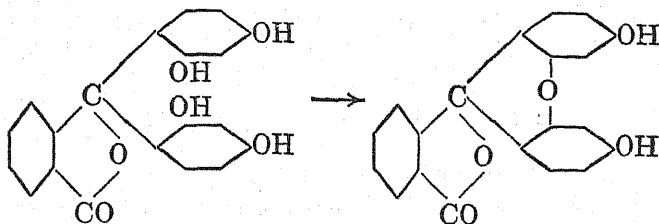
Phenolphthalein is a colorless crystalline solid which melts at  $261^\circ$ . It dissolves readily in alcohol, but it is only slightly soluble in water. It is used in medicine as a laxative.

*Fluoran.* Condensation of phenol with phthalic anhydride occurs to some extent in the *ortho* position, and the resulting phthalein loses water spontaneously, forming an oxygen linkage between the rings :

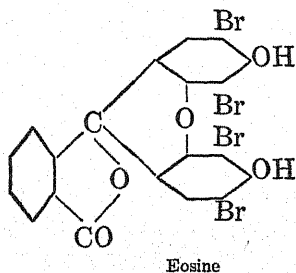


*Fluorescein.* Resorcin couples with phthalic anhydride, the point of attachment being *ortho* to one and *para* to the other

of the hydroxyl groups. At the same time water is eliminated from the *ortho* hydroxyl groups and fluorescein is produced :

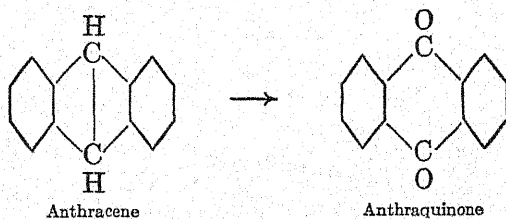


An alkaline solution of the dye appears green by reflected light and red by transmitted light. It is easily brominated, being thereby converted into the beautiful red dye eosine,



### ALIZARIN DYES

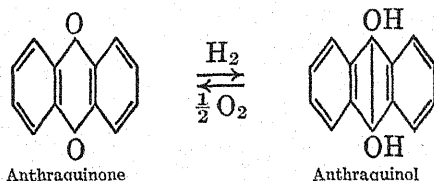
Nitric acid oxidizes anthracene to anthraquinone :



The structure of anthraquinone is established by its synthesis from phthalic anhydride and benzene in the presence of aluminum chloride, and by a study of the oxidation products of its derivatives.

Anthraquinone is a yellow crystalline substance which melts at 285°. When warmed with zinc dust in alkaline solution, it is reduced to anthraquinol, the sodium salt of which has a

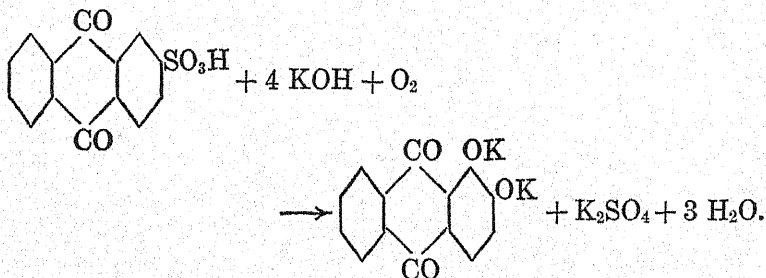
deep red color. When the red solution is shaken with air, the color fades rapidly, owing to atmospheric oxidation.



The most important derivative of anthraquinone is alizarin, a compound that forms, with metallic oxides, beautiful, insoluble dyes. Cloth to be dyed is immersed in a solution of a salt that is readily hydrolyzed. It is then steamed to hydrolyze the salt and deposit on the textile fibers a film of the metallic oxide. The mordanted cloth is then immersed in a solution or suspension of alizarin. The color produced in the fiber depends upon the mordant used. Aluminum and tin oxides yield red colors; calcium oxide, blue; ferric oxide, violet-black; and chromium oxide, a claret color.

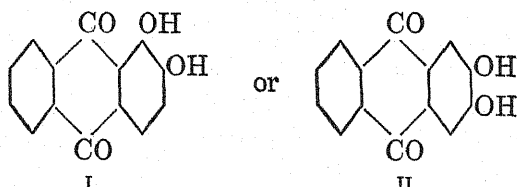
Alizarin was formerly obtained from madder roots, and was the most highly prized vegetable dye known to the ancients. During the first half of the nineteenth century the annual production of madder was approximately 70,000 tons. In 1869 alizarin was synthesized by Graebe and Liebermann, and independently by Perkin. It is now made in large quantities by modifications of their methods, and, as a result, the cultivation of madder has been abandoned.

Sulfuric acid acts upon anthraquinone to produce  $\beta$ -anthraquinone sulfonic acid,\* and this, when fused with potassium hydroxide, in the presence of air, yields a salt of alizarin:



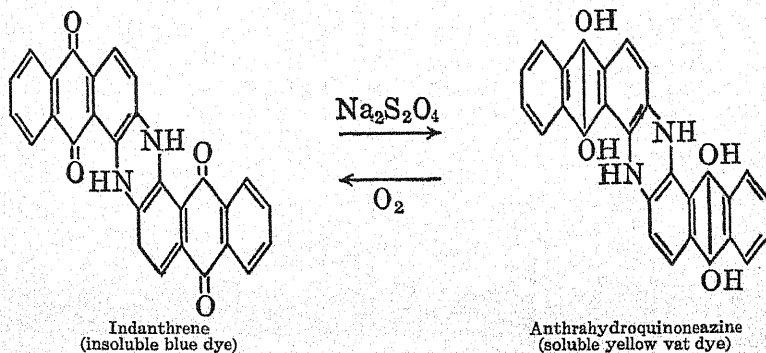
\* An  $\alpha$ -sulfonic acid is produced when the sulfonation is catalyzed by a mercury salt. Both sulfonic acids are formed in any case, but the two reactions are not equally catalyzed by the mercury salt.

The presence of two hydroxyl groups in alizarin is proved by its analysis and by its formation from phthalic anhydride and catechol. The hydroxyl groups must occupy *ortho* positions, as they do in catechol, but the method of preparation does not settle the question as to whether the two hydroxyl groups are in  $\alpha$ - $\beta$  or in  $\beta$ - $\beta$  positions :



Alizarin forms two mononitro derivatives, and in each case the nitro group enters the ring to which the hydroxyl groups are attached, for on oxidation each yields phthalic acid and not a nitrophthalic acid. The ring containing the two hydroxyl groups is very susceptible to further oxidation, even though the same ring is nitrated. From formula II only one mononitro compound could be made by substitution in the oxidized ring, but two isomeric nitroalizarins would be expected from formula I. Alizarin is, therefore,  $\alpha$ - $\beta$ -dihydroxyanthraquinone, corresponding to formula I.

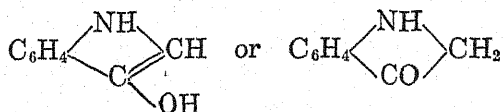
*Indanthrene*, a dark blue dye, is produced when  $\beta$ -aminoanthraquinone is fused with potassium hydroxide and sodium nitrate. It is very stable, resisting the action of oxidizing agents, acids, and alkalis, even at temperatures above  $300^{\circ}$ . It is reduced by sodium hydrosulfite in alkaline solution to a hydroxy derivative, which is a valuable vat dye. A vat dye is one that develops its color in the fiber by atmospheric oxidation after the fabric is removed from the dye bath.



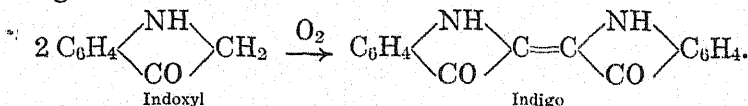


## THE INDIGOID DYES

*Indigo*, obtained from the leaves of indigo plants, has been known for many centuries. Its value depends not only upon its beautiful blue color but also upon its stability. It is not changed by acids nor alkalies nor is it faded by light. It occurs in the plant as a glucoside, indican,  $C_{14}H_{17}O_6N$ , which, in the presence of an enzyme occurring with it, is hydrolyzed by warm water to dextrose,  $C_6H_{12}O_6$ , and indoxyl,



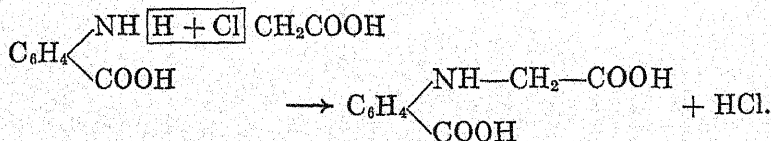
Indoxyl, in alkaline solution, is readily oxidized by the air to indigo:



The commercial method of preparing the dye from natural sources consists of leaching the leaves of the plant with luke-warm water, rendering the aqueous extract alkaline by the addition of limewater, and churning the alkaline solution with paddle wheels to aërate and thus oxidize it. Extraction with boiling water yields the unhydrolyzed glucoside, for the activity of the enzyme is destroyed at that temperature.

Since 1900 the dye has been produced synthetically, and thousands of acres of land in India, Japan, and South America, formerly devoted to the production of indigo plants, are now cultivated for the production of other crops.

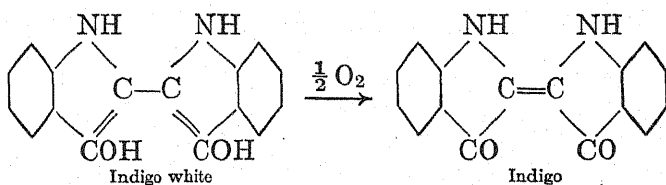
The first successful commercial synthesis of indigo was accomplished by a reaction between anthranilic acid (*ortho*-aminobenzoic acid) and chloroacetic acid:



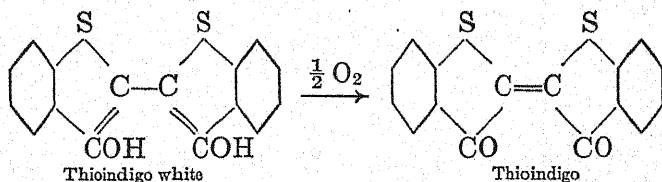
The product formed (phenylglycine-*o*-carboxylic acid), when fused with sodium hydroxide, yields indoxyl, carbon dioxide,

and water. The indoxyl is changed to indigo by oxidation, as shown above.

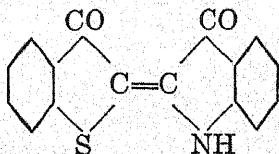
Indigo is reduced in an alkaline solution of calcium hydrosulfite ( $\text{CaS}_2\text{O}_4$ ) and by other reducing agents with the production of a colorless soluble product known as indigo white. Textiles are soaked in solutions of indigo white, then exposed to the air. The color develops in the fibers of the cloth through atmospheric oxidation during the process of drying. Deep shades are produced by repeating the operation several times.



Thioindigo is made from thiosalicyclic acid and chloroacetic acid by reactions analogous to those given for the production of indigo. It is reduced to a colorless soluble compound known as thioindigo white, which is changed by atmospheric oxidation to an insoluble red dye.



*Ciba violet* is a representative of a group of dyes in which half the molecule is constituted like indigo and half like thioindigo. It is a vat dye, developing a color between the red of thioindigo and the blue of indigo. It has the structure

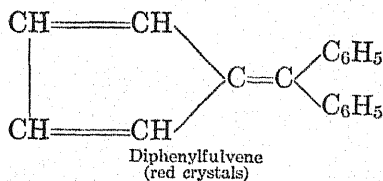
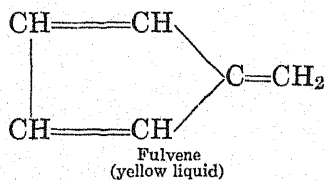


## STRUCTURE AND COLOR \*

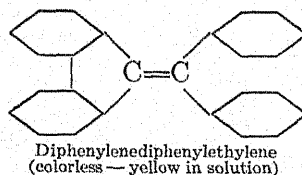
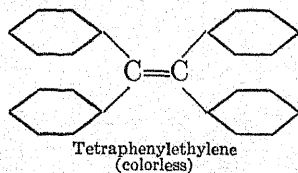
The indigoid dyes are characterized by the group  $>C=C<$  between various types of condensed rings. The azo dyes have the group  $-N=N-$  between aromatic radicals. Each triphenylmethane dye has a benzene nucleus in the quinoid form,  $=\text{C}_6\text{H}_4=$ . These groups were classified by Witt† as chromophores (color-producers). To this list should be added the

groups  $-\text{NO}_2$ ,  $-\text{NO}$ ,  $-\text{N}(\text{O})-\text{N}-$ ,  $-\text{CO}-\text{CO}-$ ,  $>C=N-$ , and  $>C=C\begin{matrix} \text{C=} \\ \text{C=} \end{matrix}$

Many colorless compounds contain one or more of these groups. The presence of a chromophore alone does not insure the appearance of color, but it is generally possible to make colored derivatives of compounds containing one or more of these groups. The fulvenes contain the last member of the above list of chromophores.

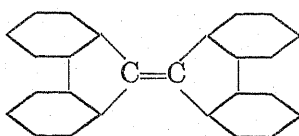


Condensed cyclic nuclei in connection with the ethylene group usually produce colored bodies. An example of the result of condensing, or tying together, aromatic nuclei is found in the following derivatives of ethylene:



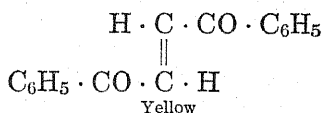
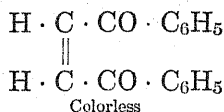
\* For an explanation of the origin of color based upon the electron theory, see G. N. Lewis, *J. Am. Chem. Soc.*, **38**, 783 (1916).

† O. N. Witt, *Ber.*, **21**, 325 (1888).

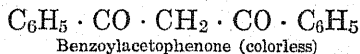
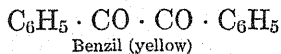
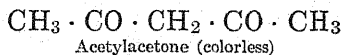
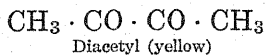


Bidiphenylene-ethylene  
(red crystals—red in solution)

Any change in the stereochemical structure of a molecule modifies the character of its absorption spectrum. We have, for example, a colored and a colorless dibenzoyl ethylene; they are geometrical isomers:

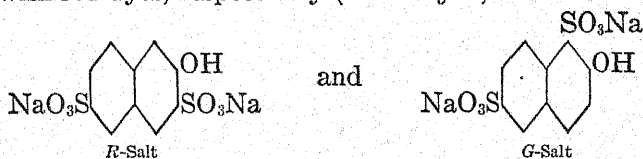


Two carbonyl groups, if adjacent, impart color to the molecule; but if separated by one or more carbon atoms, this property disappears:



To produce a red azo dye, at least one of the groups attached to the diazo nitrogen atoms must be heavier than a phenyl radical, as, for example, a naphthol or naphthylamine residue. Nearly all aliphatic azo compounds are colored, but they do not act as dyes on textiles.

The trade names *R-salt* and *G-salt* are applied to the salts of  $\beta$ -naphthol disulfonic acids, to indicate that these naphthol derivatives couple with diazonium salts to form pure red and yellowish red dyes, respectively (*rot* and *gelb*).



A group that modifies the properties of a colored compound in such a way as to make it a dye is called an auxochrome group. Azobenzene is colored, but it fails to dye textiles. Aminoazobenzene and hydroxyazobenzene are yellow dyes.

The auxochrome may also contribute to the determination of color or shade. Naphthylaminesulfonic acid and benzidine yield a pure red dye, whereas naphtholsulfonic acid and benzidine yield a reddish blue dye.

With one amino group *para* to the methane carbon in triphenylmethane we have an orange-red dye. With two rings so modified the color changes to violet, and with an amino group in the *para* position in each of the three benzene rings we have the bluish red pararosaniline. When six methyl groups are substituted for the six amino hydrogen atoms in pararosaniline, crystal violet is produced. The introduction of three phenyl radicals in pararosaniline (one phenyl radical being substituted for a hydrogen atom in each of the three amino groups) changes the color to blue.

## THE PROTEINS

Compounds known as proteins constitute the major part of the solid matter in the skin, muscle, nerve, blood, hair, and nail of the animal organism. They occur also as essential constituents of every plant. They are of the utmost importance to all forms of life. No substitution can be made for proteins in the diet. They are necessary for the continuance of life.

The molecular weights of proteins have not been determined with precision, and we are hardly justified in assigning definite molecular formulas even to the crystalline proteins that represent the purest types known. The ordinary criteria of purity (for example, sharp melting point, melting point unchanged by recrystallization, constant boiling point, and so on) cannot be applied, for proteins decompose before they melt. The best that can be done is to secure a homogeneous sample that can be recrystallized or reprecipitated without change in composition.

Many proteins are soluble in water, but the depression of the freezing point and elevation of the boiling point due to a dissolved protein never exceed a few hundredths of a degree, and the probable experimental error amounts to a large percentage of the total observed change.

We have chemical means of fixing minimum values of the molecular weights of some proteins; and these values in some cases agree with estimates made on the basis of measurements of the physical properties of their solutions. Hæmoglobin contains 0.33 per cent of iron. In one molecule of hæmoglobin there cannot be less than one atomic weight of iron. From the proportion  $0.33 : 100 = 56 : M$ , the minimum value for the molecular weight,  $M$ , is 17,000. It contains sulfur also (0.38 per cent). Cystine has been identified as one of the products formed when hæmoglobin is hydrolyzed, and cystine contains two atoms of sulfur. There must be at least two atoms of sulfur in the hæmoglobin molecule. From the proportion  $0.38 : 100 = 64 : M$ , we have for the minimum value 16,842. A measurement based upon sedimentation equilibrium in an aqueous solution of hæmoglobin when subjected to a centrif-

ugal force gives a value of 68,000 for the molecular weight of the protein.\* Recent osmotic pressure measurements indicate that in aqueous solution at the isoelectric point the molecular weight of hæmoglobin is 68,000.† This means that each molecule of hæmoglobin contains four atoms of iron.

Egg albumin has a molecular weight of approximately 34,000, and this is considered a small protein molecule. Casein derived from milk contains cystine, and its minimum molecular weight, based upon its cystine content, is 96,000. Other analytical results indicate that the true molecular weight is probably 192,000.

Though differing widely in many chemical and physical properties, the proteins are remarkably similar in composition. Most of them are composed of only half a dozen elements, and the relative proportions of these few elements vary between narrow limits. The minimum and maximum values are as follows:

|                    | PER CENT |                          | PER CENT |
|--------------------|----------|--------------------------|----------|
| Carbon . . . . .   | 50-55    | Sulfur . . . . .         | 0-5      |
| Oxygen . . . . .   | 19-25    | Phosphorus . . . . .     | 0-1      |
| Nitrogen . . . . . | 15-19    | Other elements . . . . . | 0-1      |
| Hydrogen . . . . . | 5-8      |                          |          |

It was realized more than a century ago that the only hope of securing an insight into the nature of the proteins was by decomposition of the complex molecules and identification of the simpler groups thus produced. The early researches were directed toward the decomposition products obtained by fusion with alkali or by oxidation with nitric acid or with potassium permanganate.

In 1820 Braconnot hydrolyzed a protein by boiling it with dilute sulfuric acid and he identified glycine (aminoacetic acid) as one of the hydrolysis products. This was the first important step towards the solution of the problem. Hydrolysis of a protein is accomplished in several ways: (1) boiling in acid solution; (2) boiling in alkaline solution; (3) action of superheated steam; (4) action of enzymes. Twenty amino acids have been definitely identified as constituents of the proteins. Some proteins contain all of them. In each of these acids an amino group ( $\text{NH}_2$ ) or an imino group ( $\text{NH}$ ) is attached to an  $\alpha$ -carbon atom, that is, a carbon atom adjacent to the carboxyl group.

\* T. Svedberg and Robin Fahraeus, *J. Am. Chem. Soc.*, 48, 430 (1926).

† G. S. Adair, *Proc. Roy. Soc. London, Division B*, 98, 523 (1925).

## AMINO ACIDS

1. *Glycine*:  $\text{CH}_2\text{NH}_2 \cdot \text{COOH}$
2. *Alanine*:  $\text{CH}_3 \cdot \text{CHNH}_2 \cdot \text{COOH}$
3. *Valine*:  $\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{CH} \cdot \text{CHNH}_2 \cdot \text{COOH}$
4. *Leucine*:  $\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{CH} \cdot \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH}$
5. *Isoleucine*:  $\begin{array}{c} \text{CH}_3 \\ \text{C}_2\text{H}_5 \end{array} \text{CH} \cdot \text{CHNH}_2 \cdot \text{COOH}$
6. *Phenylalanine*:  $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH}$
7. *Tyrosine*:  $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH}$
8. *Serine*:  $\text{CH}_2\text{OH} \cdot \text{CHNH}_2 \cdot \text{COOH}$
9. *Cystine*:  $\text{HOOC} \cdot \text{CHNH}_2 \cdot \text{CH}_2 \cdot \text{S} \cdot \text{S} \cdot \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH}$
10. *Aspartic acid*:  $\text{HOOC} \cdot \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH}$
11. *Glutamic acid*:  $\text{HOOC} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH}$
12.  $\beta$ -*Hydroxyglutamic acid*:  $\text{HOOC} \cdot \text{CH}_2 \cdot \text{CHOH} \cdot \text{CHNH}_2 \cdot \text{COOH}$
13. *Arginine*:  $\text{HN}=\text{C} \begin{array}{c} \text{NH}_2 \\ \text{NH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH} \end{array}$
14. *Lysine*:  $\text{H}_2\text{N} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH}$
15. *Histidine*:  $\begin{array}{c} \text{CH} \\ \text{N} \quad \text{NH} \\ \text{CH}=\text{C} \end{array} \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH}$
16. *Proline*:  $\begin{array}{c} \text{CH}_2-\text{CH}_2 \\ | \quad | \\ \text{CH}_2 \quad \text{CHCOOH} \\ | \quad | \\ \text{NH} \end{array}$
17. *Oxyproline*:  $\begin{array}{c} \text{CH}_2-\text{CHOH} \\ | \quad | \\ \text{CH}_2 \quad \text{CHCOOH} \\ | \quad | \\ \text{NH} \end{array}$
18. *Tryptophane*:  $\begin{array}{c} \text{C}-\text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH} \\ | \\ \text{C}_6\text{H}_4 \quad \text{CH} \\ | \\ \text{NH} \end{array}$
19. *Thyroxine*:\*  $\text{HO} \begin{array}{c} \text{I} \\ | \\ \text{C}_6\text{H}_4 \\ | \\ \text{I} \end{array} \text{O} \begin{array}{c} \text{I} \\ | \\ \text{C}_6\text{H}_4 \\ | \\ \text{I} \end{array} \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH}$
20. *Methionine*:†  $\text{CH}_3 \cdot \text{S} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH}$

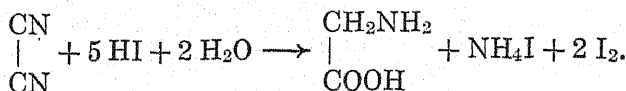
\* Isolated by E. C. Kendall. Synthesized by C. R. Harrington and G. Barger. See *Biochem. J.*, 21, 169 (1927); E. C. Kendall, *Thyroxine*, Chemical Catalog Co. (1929).

† Isolated by J. H. Mueller. Synthesized by Barger and Coyne. See H. B. Vickery and T. B. Osborne, *Physiol. Rev.*, 8, 409 (1928).

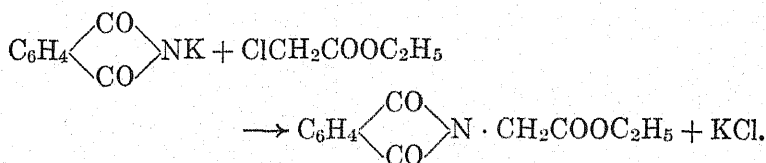


*Glycine*, aminoacetic acid,  $\text{CH}_2\text{NH}_2 \cdot \text{COOH}$ , was first obtained from gelatin by boiling with sulfuric acid. It occurs in very small quantities in vegetable proteins and has not been detected at all in casein nor in albumin. It is abundant in gelatin and in silk fibroin. Glycine melts and decomposes at  $233^\circ$ .

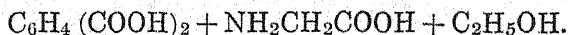
Cyanogen is half reduced and half hydrolyzed by hydriodic acid and is thereby converted into glycine:



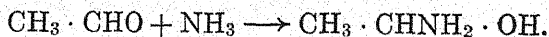
Glycine may be prepared also by Gabriel's synthesis from potassium phthalimide and chloroacetic ester:



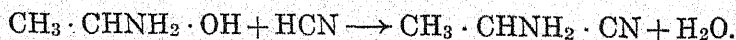
On hydrolysis this derivative of phthalimide yields phthalic acid, glycine, and ethyl alcohol:



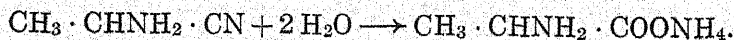
*Alanine*,  $\alpha$ -aminopropionic acid,  $\text{CH}_3 \cdot \text{CHNH}_2 \cdot \text{COOH}$ , is widely distributed, being found in almost every known protein. It was synthesized by Strecker (1850) thirty years before it was identified as a protein constituent. His method, which follows, has been applied with equal success in the preparation of some other amino acids. By treatment with ammonia an aldehyde is converted into an aldehyde ammonia. In the preparation of alanine acetaldehyde is used:



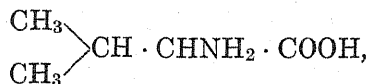
The hydroxyl group in this addition product is replaced by CN through the agency of hydrogen cyanide:



The cyanide is then hydrolyzed by boiling it with an acid or with a solution of potassium hydroxide:

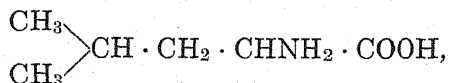


*Valine*,  $\alpha$ -aminoisovaleric acid,



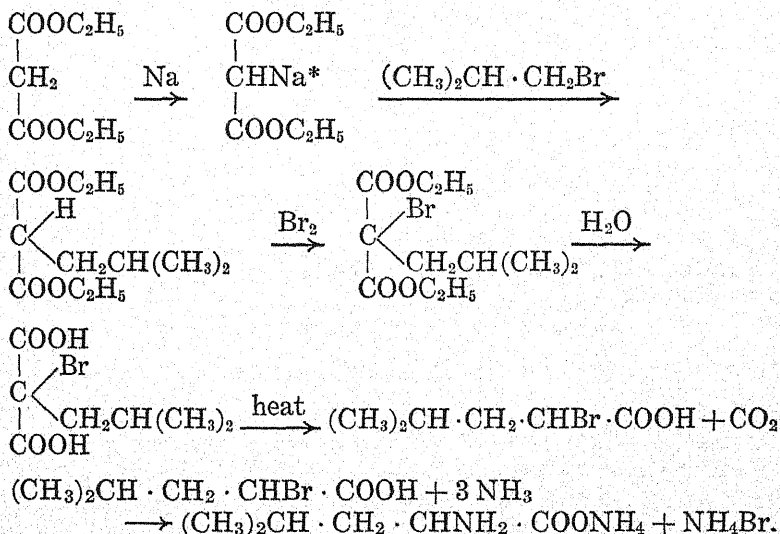
was isolated from the hydrolysis products of proteins, and its empirical formula was determined, as early as 1856. Ten years later it was synthesized from valeric acid; but the identity of the natural and synthetic products was not established until 1906. Valine melts and decomposes at  $298^\circ$ .

*Leucine*,  $\alpha$ -aminoisobutylic acid,



occurs in very large quantities in animal and vegetable proteins. It is found also in the free state in some organs of the body and in the seeds of many plants. It constitutes 6.6 per cent of gliadin, 19 per cent of zein, 14 per cent of edestin, and more than 9 per cent of casein. It was isolated from meat, cheese, silk, horn, and albumin in the first half of the nineteenth century.

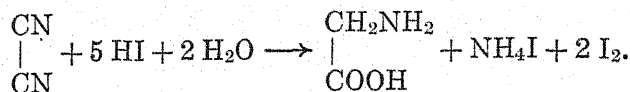
The malonic ester synthesis gives a satisfactory yield:



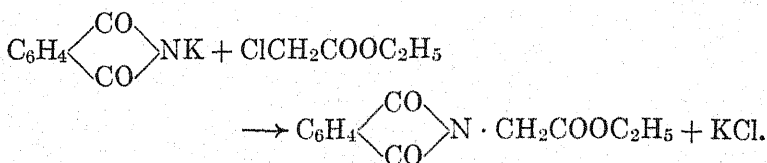
\* For many years the formula of sodiummalonic ester has been written in this form. It is probably incorrect. (See pages 426-427.)

*Glycine*, aminoacetic acid,  $\text{CH}_2\text{NH}_2 \cdot \text{COOH}$ , was first obtained from gelatin by boiling with sulfuric acid. It occurs in very small quantities in vegetable proteins and has not been detected at all in casein nor in albumin. It is abundant in gelatin and in silk fibroin. Glycine melts and decomposes at  $233^\circ$ .

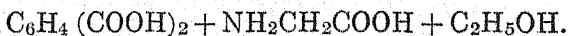
Cyanogen is half reduced and half hydrolyzed by hydriodic acid and is thereby converted into glycine:



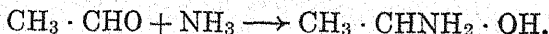
Glycine may be prepared also by Gabriel's synthesis from potassium phthalimide and chloroacetic ester:



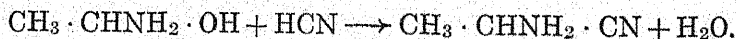
On hydrolysis this derivative of phthalimide yields phthalic acid, glycine, and ethyl alcohol:



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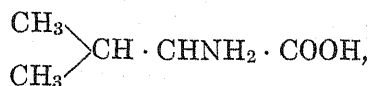
The hydroxyl group in this addition product is replaced by CN through the agency of hydrogen cyanide:



The cyanide is then hydrolyzed by boiling it with an acid or with a solution of potassium hydroxide:

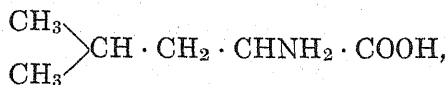


*Valine*,  $\alpha$ -aminoisovaleric acid,



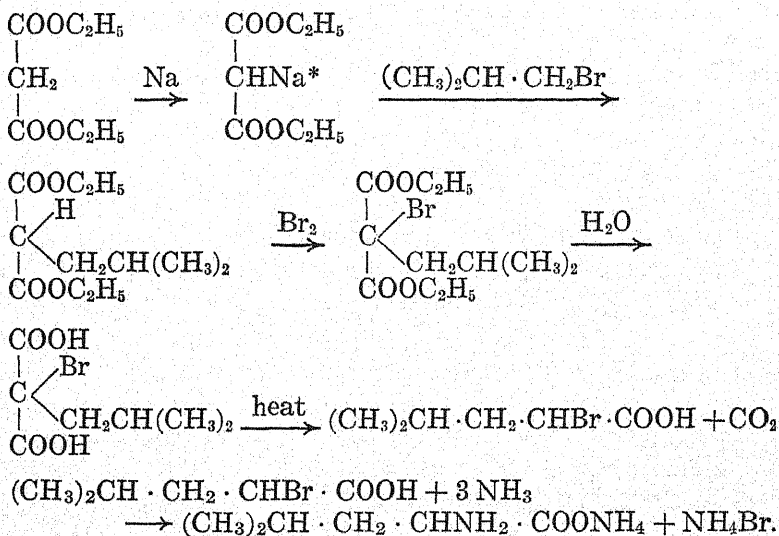
was isolated from the hydrolysis products of proteins, and its empirical formula was determined, as early as 1856. Ten years later it was synthesized from valeric acid; but the identity of the natural and synthetic products was not established until 1906. Valine melts and decomposes at  $298^\circ$ .

*Leucine*,  $\alpha$ -aminoisobutylacetic acid,



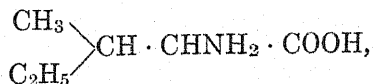
occurs in very large quantities in animal and vegetable proteins. It is found also in the free state in some organs of the body and in the seeds of many plants. It constitutes 6.6 per cent of gliadin, 19 per cent of zein, 14 per cent of edestin, and more than 9 per cent of casein. It was isolated from meat, cheese, silk, horn, and albumin in the first half of the nineteenth century.

The malonic ester synthesis gives a satisfactory yield:



\* For many years the formula of sodiomalonic ester has been written in this form. It is probably incorrect. (See pages 426-427.)

*Isoleucine*,  $\alpha$ -amino- $\beta$ -methylvaleric acid,



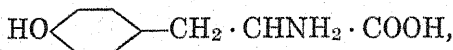
is very similar to leucine in all properties and may be synthesized in the same way, with the substitution of secondary butyl bromomethane for the isobutyl derivative used in the equations given above. Isoleucine has been prepared also by the action of ammonia on the corresponding chloro acid and from valeraldehyde through the agency of ammonia and hydrogen cyanide.

*Phenylalanine*,  $\beta$ -phenyl- $\alpha$ -aminopropionic acid,



is found among the hydrolysis products of almost all proteins. Its constitution was proved by Erlenmeyer and Lipp, who produced it from phenylacetaldehyde by an application of the cyanhydrin synthesis.

*Tyrosine*,  $\beta$ -parahydroxyphenyl- $\alpha$ -aminopropionic acid,



is the first of the amino acids to crystallize from solutions of the hydrolysis products of proteins. Cystine is almost equally insoluble and the two are usually obtained together. Their separation is accomplished by dissolving the tyrosine in dilute nitric acid or by precipitating the cystine in the form of its mercury salt. Tyrosine was discovered by Liebig among the products obtained by fusing cheese with potassium hydroxide. It crystallizes in fine glossy needles.\*

*Serine*,  $\alpha$ -amino- $\beta$ -hydroxypropionic acid,

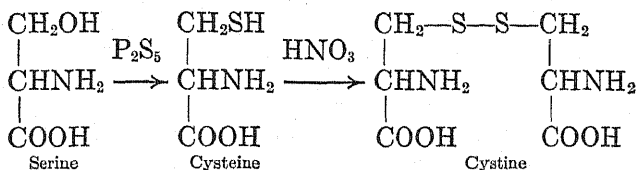


is abundant in silk glue. Serine crystals melt and decompose at  $246^\circ$ .

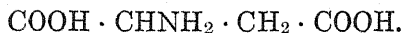
*Cystine*, di( $\beta$ -thio- $\alpha$ -aminopropionic acid), occurs in great abundance in hair, wool, and horn. It is present in all sulfur-containing proteins and is the only source of sulfur in many

\* For methods of synthesizing this and the following amino acids and for a more complete discussion of all hydrolysis products of the proteins see Plimmer's "Chemical Constitution of the Proteins."

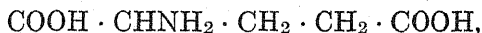
of them. Cystine decomposes at 258°. It may be synthesized from serine as follows:



*Aspartic acid*, or aminosuccinic acid, occurs in very limited quantities in most proteins. Its amide, asparagine, is abundant in asparagus and in peas and beans. The aspartic acid derived from proteins is laevorotatory. It melts at 270°. Its formula is

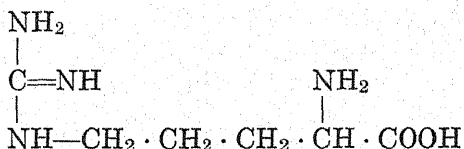


*Glutamic acid*,  $\alpha$ -aminoglutaric acid,



occurs in many seeds. Gliadin, from wheat, is 43 per cent glutamic acid. Zein, from corn, is 26 per cent, and edestin, from hemp seed, is more than 18 per cent glutamic acid. Glutamic acid melts at 198°.

*Arginine*,  $\alpha$ -amino- $\delta$ -guanidine valeric acid, has the structure



It is a basic substance. It turns litmus blue and forms stable carbonates. The dextro form occurs in nature. Both optically active forms have been prepared in the laboratory.

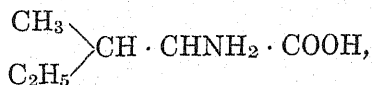
*Lysine*,  $\alpha$ - $\epsilon$ -diaminocaproic acid,



has not been obtained in crystalline form. It yields a crystalline salt with picric acid and is usually isolated in this form.

Feeding experiments indicate that lysine is of supreme importance to the growing animal organism. Arrested development due to insufficient lysine in the diet has been reported by many investigators.

*Isoleucine*,  $\alpha$ -amino- $\beta$ -methylvaleric acid,



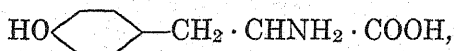
is very similar to leucine in all properties and may be synthesized in the same way, with the substitution of secondary butyl bromomethane for the isobutyl derivative used in the equations given above. Isoleucine has been prepared also by the action of ammonia on the corresponding chloro acid and from valeraldehyde through the agency of ammonia and hydrogen cyanide.

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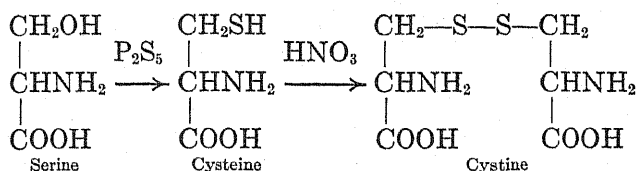


is abundant in silk glue. Serine crystals melt and decompose at  $246^\circ$ .

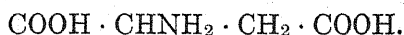
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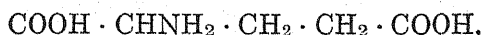
of them. Cystine decomposes at 258°. It may be synthesized from serine as follows:



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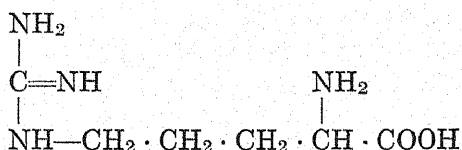


*Glutamic acid*,  $\alpha$ -aminoglutaric acid,



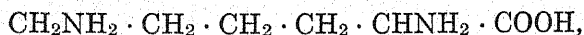
occurs in many seeds. Gliadin, from wheat, is 43 per cent glutamic acid. Zein, from corn, is 26 per cent, and edestin, from hemp seed, is more than 18 per cent glutamic acid. Glutamic acid melts at 198°.

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It is a basic substance. It turns litmus blue and forms stable carbonates. The dextro form occurs in nature. Both optically active forms have been prepared in the laboratory.

*Lysine*,  $\alpha$ - $\epsilon$ -diaminocaproic acid,

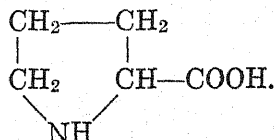


has not been obtained in crystalline form. It yields a crystalline salt with picric acid and is usually isolated in this form.

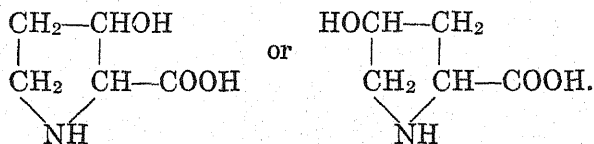
Feeding experiments indicate that lysine is of supreme importance to the growing animal organism. Arrested development due to insufficient lysine in the diet has been reported by many investigators.



*Proline*,  $\alpha$ -pyrrolidine carboxylic acid, is the only member of the group which dissolves freely in alcohol. It is a heterocyclic compound having the structure



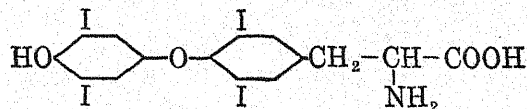
*Oxyproline* has been isolated from very few proteins and has never been found in large amounts. It is represented by one of the following formulas :



The position of the hydroxyl group has not been determined.

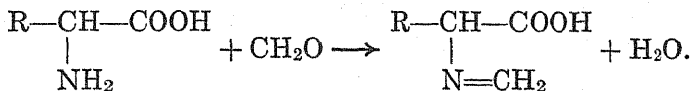
*Tryptophane*,  $\beta$ -indoxyl- $\alpha$ -aminopropionic acid, is destroyed by acids and by heat and therefore does not appear among the hydrolysis products of proteins unless the decomposition is effected at ordinary temperatures by the action of enzymes. Feeding experiments have demonstrated the fact that animals deprived of tryptophane die within a few weeks. Zein, found in corn, and gliadin of wheat contain no tryptophane. These substances alone, therefore, fail to supply the protein requirements in the diet.

*Thyroxine*, a constituent of the thyroid gland, is an amino acid. Myxoedema and goiter are among the disorders that are due to thyroid deficiency. Thyroxine has been synthesized. It has the following structure :



The amino acids are almost neutral compounds, since the carboxyl group is virtually neutralized by the  $\alpha$ -amino group. Henriques and Sørensen devised a method of rendering the amino group inactive, thereby making it possible to determine the number of carboxyl groups in any given sample by the

usual analytical methods.\* Formaldehyde is added to the solution and each amino acid molecule reacts with it as follows:



Phenolphthalein is then added as an indicator, and the solution is titrated with a standardized solution of sodium hydroxide. A correction is necessary if an ammonium salt is present, for in this case the following reaction occurs:

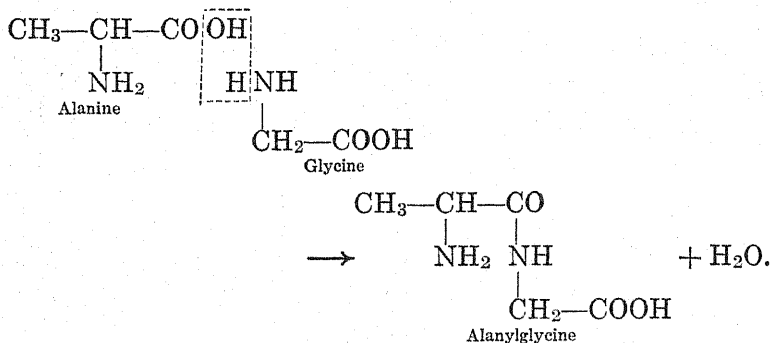


The hydrogen ions produced in this reaction neutralize part of the base used in the titration.

### STRUCTURE OF THE PROTEINS

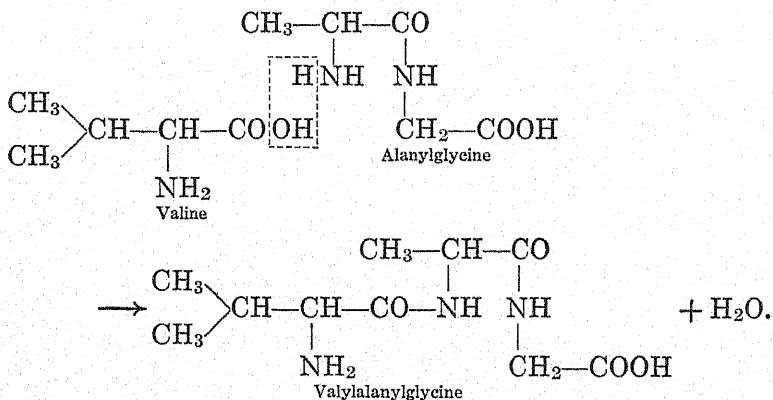
When hydrolyzed, the *simple* proteins yield amino acids only. More complex proteins yield amino acids and other products. Carbohydrates, phosphoric acid, purines, pyrimidines, and lecithins are among the hydrolysis products of some proteins. The proteins are amphoteric substances. In the presence of bases they act like weak acids, forming salts in which the protein constitutes the negative ion. When mixed with acids they act like weak bases, forming salts in which the protein is the positive ion; but the quantity of acid or of base that can be neutralized by a protein is insignificant compared with the neutralizing capacity of the amino acids which the protein yields on hydrolysis. In the protein molecule the amino acids are combined in such a way as to neutralize the basic amino groups and the acidic carboxyl groups. At the beginning of the twentieth century F. Hofmeister and Emil Fischer independently reached the conclusion that these acids are linked together through the amino and carboxyl groups. Suppose, for example, that a molecule of water is eliminated through a reaction between the amino group of glycine and the carboxyl group of alanine as shown in the following equation:

\* V. Henriques and S. P. L. Sørensen, *Z. physik. Chem.*, **64**, 120 (1908).



The product, alanylglycine, is a dipeptide—a compound derived from two amino acids through the loss of one molecule of water. The two units are held together through a —CO—NH— group. This is called a peptide linkage. It is the same type of linkage that occurs in an amide, R—CO—NH<sub>2</sub>. A dipeptide is a substituted amide.

A reaction between the amino group of this dipeptide and the carboxyl group of an amino acid gives rise to a tripeptide :



A tripeptide is composed of three amino acid molecules less two molecules of water. In general, a polypeptide is composed of  $n$  amino acid molecules less  $n - 1$  molecules of water, the linkage, in each case, involving an amino group of one unit and a carboxyl group of another. It is possible to synthesize polypeptides, but not by a simple dehydration of the amino acids as indicated above. The simple proteins are polypeptides of high molecular weights.

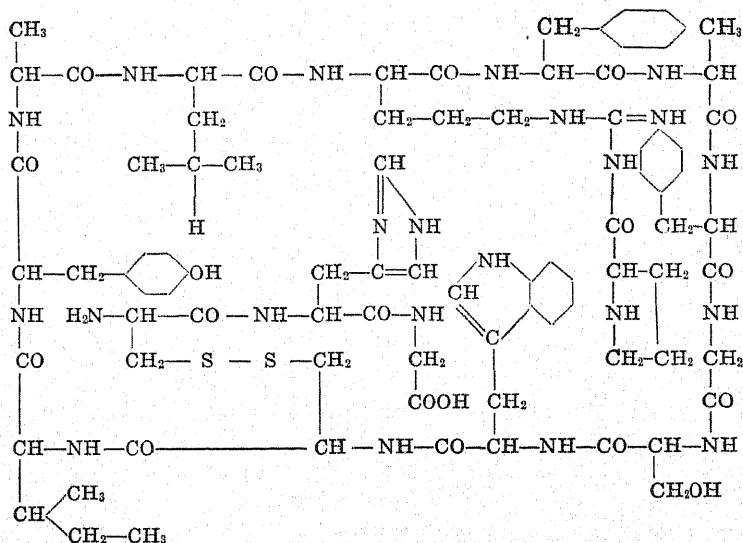
In the proteins most of the amino acid linkages are of the amide type, but there is abundant evidence that not all the amino acid units are linked through the  $\text{—CO—NH—}$  groups. Some cyclic hydrolysis products of proteins contain groups in which three carbon atoms are attached to the same nitrogen atom. We know nothing of the nature of the union between the amino acid units and the carbohydrates or the nucleic acids that are constituents of many conjugated proteins. It is beyond the scope of this book to describe all the types of hydrolysis products that have been derived from the proteins or to outline all the possible modes of union between these units.\*

The general formula of a simple protein may be written as follows:



in which each R represents the residue beyond the  $\alpha$ -carbon atom of an amino acid.

To be more specific, a protein molecule may be represented by a structure of the following type:

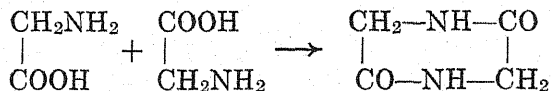


\* For good discussions of this subject see Emil Klarmann, *Chem. Rev.*, **4**, 51 (1927); Andrew Hunter, *Trans. Roy. Soc., Canada*, **19**, 1 (1925); H. B. Vickery and Thomas B. Osborne, *Physiol. Rev.*, **8**, 393 (1928); L. M. Chapman, D. M. Greenberg, and C. L. A. Schmidt, *J. Biol. Chem.*, **72**, 707 (1927); Edwin J. Cohn, *Physiol. Rev.*, **5**, 349 (1925).

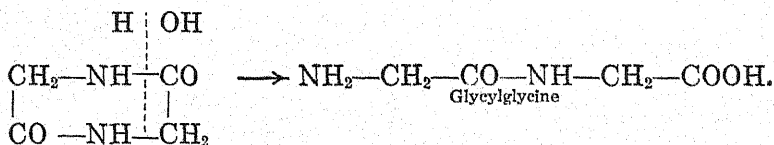
This hypothetical tetradecapeptide may not actually exist. The formula is intended merely to illustrate the polypeptide type of structure.

### SYNTHESIS OF POLYPEPTIDES

When amino acids are heated with dehydrating agents, ring compounds are produced by the elimination of water from the amino group of one molecule and the carboxyl group of another. These products belong to the class of compounds known as diketopiperazines. Taking glycine as the simplest example, the formation of the dehydration product is represented as follows:



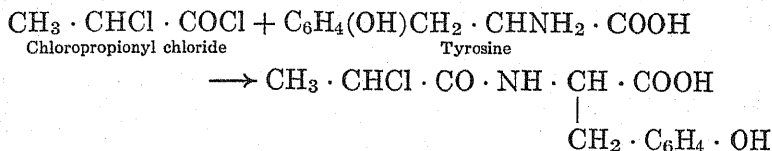
When warmed with dilute sodium hydroxide or concentrated hydrochloric acid, this product is partly hydrolyzed.\* One molecule of water is added, and the bond between carbon and nitrogen in one of the —CO—NH— groups is broken. The ring structure is thus destroyed.



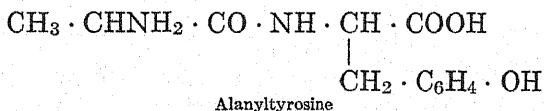
Since glycylglycine is itself an amino acid, it might be expected to yield an anhydride which, by partial hydrolysis, could be converted into a tetrapeptide, or it might form a mixed anhydride with a single molecule of any amino acid and give rise to a tripeptide. Attempts to build up polypeptides by this method have failed. Dipeptides are easily made; tripeptides are formed in a few instances, but the limits are soon reached, and the hope of synthesizing proteins in this manner has been abandoned. A better method, based upon reactions of chloro acid chlorides and amino acids, was developed by Fischer. An acid chloride is prepared by the action of phosphorus trichloride on the free organic acid. Chlorine acts upon the chloride of a saturated acid, substituting chlorine for hydrogen

\* Prolonged heating results in complete hydrolysis to amino acids.

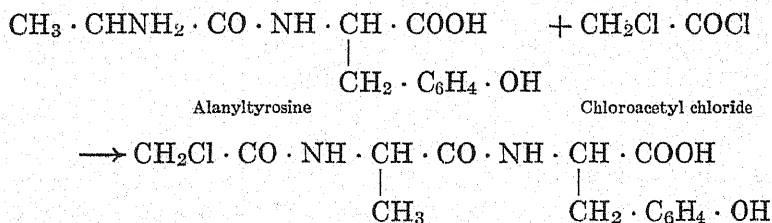
in the  $\alpha$  position. The chloro acid chlorides thus produced react energetically with free amino acids, eliminating hydrochloric acid:



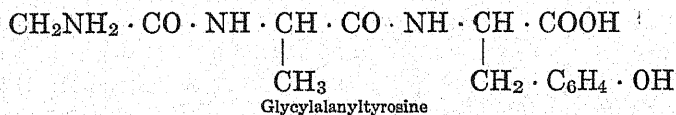
The remaining chlorine atom may be replaced by an amino group through the agency of ammonia. The compound is dissolved in an excess of a 25 per cent aqueous solution of ammonia and held at a constant temperature until most of the chlorine has been displaced. This usually requires from twenty-four to eighty hours. The temperature range for this work is 25° to 60°. In this case the product would be the dipeptide alanyltyrosine.



The dipeptide acts like a free amino acid on other chloro acid chlorides :



On treatment with ammonia this yields a tripeptide:



It is theoretically possible to lengthen the chain indefinitely. Experimental difficulties, however, multiply rapidly and establish practical limits. By this method, with many ingenious variations, Fischer built up an octadecapeptide (eighteen amino acid molecules combined), a compound with a molecular weight

of 1213. It was a colorless, amorphous substance which, in water, gave a highly dispersed colloidal solution with faint opalescence. Like most natural proteins, it was precipitated from solution by ammonium sulfate and by tannic acid. There can be no doubt that this compound would have been classified as a protein if it had been discovered in nature instead of appearing as a synthetic preparation. A polypeptide containing nineteen amino acid residues and having a molecular weight of 1326 was made by Abderhalden and Fodor.\*

### HYDROLYSIS OF PROTEINS

**Simple proteins.** The digestion of a protein is a natural process of hydrolysis. Artificially the same result is achieved by heating the protein with an aqueous solution of an acid or a base.

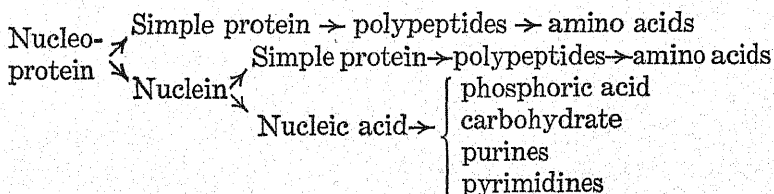
Hydrolysis of simple proteins by acids, by alkalies, or by the ferments of the alimentary tract consists in adding water molecules to the  $\text{—CO—NH—}$  groups, thus breaking the bonds between carbon and nitrogen, with the production of carboxyl and amino groups. As one after another of these groups suffers cleavage, the protein molecule is gradually broken into polypeptide fragments. It is not a regular process, resulting in a split at the center of the chain each time, nor is it a uniform erosion of the molecule through the breaking off of terminal groups. Simple and complex hydrolysis products appear together from the beginning of the proteolytic action. Pepsin of the gastric juice induces hydrolysis of proteins to a limited extent, giving rise to substances similar to the original protein in general character and composition but of lower molecular weight. These first cleavage products are known as proteoses and peptones. They differ from the parent protein only in degree of molecular complexity and a few properties dependent primarily upon the size of the molecule. Trypsin and erepsin, ferments of the intestinal tract, complete the hydrolysis. A protein, for example, may form an opalescent solution, coagulate when heated, and precipitate in the presence of ammonium sulfate. After partial hydrolysis it may form an optically clear solution and fail to coagulate on heating but retain all other properties of the original compound. The protein has been converted into proteoses. A continuation of the process results

\* Emil Abderhalden and Andor Fodor, *Ber.*, 49, 561 (1916).

in the formation of substances which still display protein characteristics but can no longer be salted out of solution by ammonium sulfate. The proteoses have been converted into peptones. As the cleavage proceeds, the units become too small to behave like proteins, yet they are more complex than single molecules of amino acids. They are polypeptides. Finally the mixture consists of free amino acids, the hydrolysis being complete.

Proteins of the diet reach the blood stream through the walls of the intestine chiefly in the form of amino acids,\* and these are recombined within the cells of the body to form the characteristic tissues of the organism. It is evident that the most satisfactory protein diet is one that supplies the different amino acids in the proportions required by the tissues they nourish. Persons who depend entirely upon a vegetable diet must ingest and eliminate excessive amounts of some protein constituents in order to secure the minimum requirement of others. As the food approaches in proximate analysis that of the tissue it builds, the waste in the energy of the system is reduced and at the same time the quantity of food required is diminished.

**Nucleoproteins.** The nucleoproteins are obtained from the nuclei of cells in plant and animal tissues and are composed of simple proteins in combination with nucleic acids. The term *nucleic acid* has a rather definite meaning although it is applied to a great variety of compounds. It refers to an acidic hydrolysis product of proteins derived from cell nuclei. It consists of phosphoric acid in combination with at least one purine base, a pyrimidine derivative, and a carbohydrate. The complete hydrolysis of a nucleoprotein is represented by the following diagram. The first cleavage is brought about by gastric digestion, and the subsequent processes are due to the action of trypsin and erepsin; or the complete degradation of the molecules can be accomplished artificially by boiling with alkali.



\* This statement is disputed by some physiologists. For discussions of the question see Cathcart's "The Physiology of Protein Metabolism" and Robertson's "Principles of Biochemistry."



The carbohydrate derived from most nucleic acids of plant origin is a pentose, *d*-ribose. This sugar, as well as several hexoses, occurs in nucleic acids of animal tissues. Methyl-pentose, a glucoside derived from pentose by replacement of a hydroxyl hydrogen atom by the methyl radical, has been identified as a constituent of a few nucleoproteins.

The purine bases found in nucleic acids almost invariably include guanine and adenine. In the pyrimidine group cystosine may be mentioned as the most widely distributed representative. Uracil is found in nearly all vegetable nucleic acids, and thymine is present in all nucleoproteins of animal origin.

**Isolation of amino acids.** The protein is hydrolyzed, usually by boiling it with 25 per cent sulfuric acid until the mixture no longer responds to the biuret test. The time required varies from a few hours to a week. The solution is then diluted with water, filtered, neutralized with barium carbonate, and separated by filtration from the precipitate of barium sulfate and excess of barium carbonate. The clear filtrate is concentrated by evaporation. The very slightly soluble acids, tyrosine and cystine, crystallize and are removed by filtration.

Diamino acids are precipitated by means of phosphotungstic acid and removed by filtration. The excess of phosphotungstic acid is removed by precipitating it with barium hydroxide, and the excess of barium is removed by means of carbon dioxide. The filtrate from these residues is saturated with hydrogen chloride, and, on standing, glutamic acid crystallizes out. The amino acids remaining in solution are esterified by the action of alcohol and hydrogen chloride. Glycine ester hydrochloride, being only slightly soluble, separates in crystalline form when the alcohol is removed by evaporation. The solution is then neutralized with potassium carbonate, and aspartic ester is extracted with ether. The remaining esters are separated into small groups by fractional distillation under reduced pressure. Fischer tabulates the fractions as follows:

|     |           |         |  |
|-----|-----------|---------|--|
| I   | 50°- 60°  | 10 mm.  | Glycine, alanine, leucine.                           |
| II  | 60°- 90°  | 10 mm.  | Leucine, valine, proline.                            |
| III | 90°-100°  | 0.5 mm. | Leucine, proline.                                    |
| IV  | 130°-180° | 0.5 mm. | Phenylalanine, glutamic acid, aspartic acid, serine. |

The fractions are separately hydrolyzed, and the free acids in each group are isolated by extraction with various solvents or by fractional crystallization of the free acids or of their copper, silver, lead, or barium salts.

### CLASSIFICATION

We do not know the order in which the amino acids are assembled nor the exact number of them in any particular molecule. We do not know the nature of the union between the amino acid groups and such other units as were mentioned

in connection with the nucleoproteins. A scientific classification cannot be made until these things have been determined. An arbitrary classification based upon proximate analyses and a few physical properties has been adopted by the American Physiological Society and the American Society of Biological Chemists. It is given below.

- I. Simple Proteins. Hydrolysis products consist of amino acids only.
  - a. *Albumins*. Soluble in water. Coagulable by heat.
  - b. *Globulins*. Insoluble in water. Soluble in neutral salt solutions.
  - c. *Glutelins*. Insoluble in neutral solvents. Soluble in dilute solutions of acids and bases.
  - d. *Prolamins*. Soluble in 70-80 per cent alcohol, insoluble in absolute alcohol, water, and other neutral solvents.
  - e. *Albuminoids*. Insoluble in all neutral solvents.
  - f. *Histones*. Basic proteins. Soluble in water. Insoluble in dilute ammonia. Form precipitates with solutions of other proteins. Coagulate when heated. Coagulum soluble in very dilute acids.
  - g. *Protamines*. Simple polypeptides — not coagulated by heat. Basic amino acids predominate in hydrolysis products.
- II. Conjugated Proteins. Hydrolysis products consist of amino acids and at least one other type of molecule.
  - a. *Nucleoproteins*. One or more protein molecules combined with nucleic acid.
  - b. *Glycoproteins*. Proteins combined with a carbohydrate not included in nucleic acid.
  - c. *Phosphoproteins*. Proteins containing phosphorus not included in nucleic acid nor in lecithins.
  - d. *Hæmoglobins*. Proteins combined with hæmatin.
  - e. *Lecithoproteins*. Proteins combined with lecithins.
- III. Derived Proteins. Cleavage products of more complex proteins.
  - a. *Proteans*. Insoluble in water. First products of hydrolytic cleavage.
  - b. *Metaproteins*. Products formed by further action of acids, alkalies, or enzymes. Soluble in dilute acids and alkalies. Insoluble in neutral solvents.
  - c. *Coagulated Proteins*. Insoluble products formed by the action of heat or alcohol on protein solutions.
  - d. *Proteoses*. Soluble hydrolysis products of proteins. Not coagulated by heat. Precipitated by saturating the solution with ammonium sulfate.
  - e. *Peptones*. Hydrolysis products. Soluble. Not coagulated by heat. Not precipitated by ammonium sulfate.
  - f. *Peptides*. Definite compounds of known structure consisting of two or more amino acids united through the amino and the carboxyl groups.

## QUALITATIVE REACTIONS

A few qualitative tests are useful in determining whether or not a compound under investigation should be classed as a protein. The following reactions are not exclusively characteristic of proteins. They are tests to which most proteins respond, but for each test substances other than proteins give the same result. If, however, the substance analyzed gives positive response to several of these tests, it may be classified as a protein.

1. *Nitric acid.* If an aqueous solution of a protein is carefully floated on the surface of concentrated nitric acid, a white precipitate forms at the junction of the two layers.

2. *Heavy metals.* Most proteins form insoluble salts of lead, copper, and mercury. The precipitate forms in acid, alkaline, or neutral solution.

3. *Alkaloid precipitants.* Phosphotungstic acid, tannic acid, picric acid, phosphomolybdic acid, potassium bismuth iodide, potassium mercuric iodide, and other reagents that precipitate the alkaloids form insoluble compounds with proteins also.

4. *Biuret reaction.* When dilute copper sulfate solution is added to an alkaline solution of a protein, a reddish violet color is produced. The appearance of the color merely indicates the presence of one of the following groups:



5. *Glyoxylic acid.* A mixture of a protein solution with glyoxylic acid (or glacial acetic acid, which always contains a little glyoxylic acid) is floated on the surface of concentrated sulfuric acid. A reddish violet ring appears at the junction of the liquid layers. The color is due to the presence of tryptophane.

6. *Xanthoproteic test.* Concentrated nitric acid applied to a protein in the solid state imparts a yellow color, which changes to orange in the presence of ammonia. The color is due to the presence of substituted benzene rings of the types found in tyrosine, tryptophane, and thyroxine.

7. *Millon's reaction.* Millon's reagent consists of a freshly prepared solution of mercury in nitric acid. It contains mercurous and mercuric nitrates and nitrous and nitric acids.

When added to a protein solution, it produces a white precipitate which turns red when heated. The color change is apparently due to the hydroxyphenyl group present in tyrosine. Phenols give the same result.

### PROTEIN SALTS

The proteins are amphoteric. Many of them form definite series of salts with acids and with bases. Casein, a typical phosphoprotein, obtained from milk by precipitation with dilute acetic acid, is a white, amorphous powder. It is insoluble in water but soluble in 50 per cent alcohol. A suspension of casein in water turns litmus red where the suspended particles touch the litmus paper, and it liberates carbon dioxide from carbonates.

The alkali salts of casein are soluble in water and may be precipitated unchanged by the addition of alcohol. Van Slyke and Bosworth prepared an insoluble salt of casein with calcium hydroxide which contained  $11.25 \times 10^{-5}$  of an equivalent of the base per gram of the protein, and another salt containing  $22.5 \times 10^{-5}$  of an equivalent of base per gram of casein. Using sodium or potassium hydroxide, they found that  $11.4 \times 10^{-5}$  of a mole of the base per gram of casein just suffices to convert the protein into a water-soluble salt. The maximum quantity of potassium hydroxide that one gram of casein will neutralize is  $182 \times 10^{-5}$  of a mole. This is almost exactly sixteen times the amount required to dissolve the protein. One gram of casein has the capacity to neutralize  $90 \times 10^{-5}$  of a mole of hydrochloric acid. One gram of egg albumin will combine with  $80 \times 10^{-5}$  of an equivalent of an acid or with  $80 \times 10^{-5}$  of an equivalent of a base.

According to Schmidt and Greenberg a protein contains a sufficient number of free carboxyl groups and hydroxyl groups to account for the maximum quantity of base that it will neutralize and a sufficient number of free amino groups and imino groups to account for its neutralization of acids. Among the amino acids found in proteins there are three basic compounds. They are arginine, histidine, and lysine. Each of these could supply an amino group for the  $\text{—CO—NH—}$  linkage and still have an imino group (NH) or an amino group ( $\text{NH}_2$ ) available for the neutralization of an acid. Similarly, aspartic, glutamic,

or oxyglutamic acid may yield one carboxyl group in an amide linkage and retain a free carboxyl group. The latter is engaged in salt formation when the protein is treated with a base. The hydroxyl group in tyrosine may also react with a base.

Protein salts are conductors of electricity. The salts formed with bases yield positive metallic ions and negative protein ions. Salts formed by treating proteins with acids yield positive protein ions and the anion of the acid used. At a certain definite hydrogen ion concentration an amphoteric substance has neither acidic nor basic properties. The hydrogen ion concentration required to establish this condition is different for different ampholytes. It is called the *isoelectric point*. At the isoelectric point any addition of hydrogen ions causes the protein to act like a base; that is, it neutralizes the acid. The addition of hydroxide ions makes the protein act like an acid — it neutralizes the base.

It is possible in many cases to follow the migration of a protein ion in an electric field by observing the moving boundary between colored and colorless regions or between clear and opalescent regions in the electrolytic cell. The colored solution of hæmoglobin can be seen to migrate toward the anode in an alkaline solution and toward the cathode in an acid solution. The isoelectric point is  $(H^+) = 2 \times 10^{-7}$ . At a hydrogen ion concentration of  $2.1 \times 10^{-5}$  of a mole per liter serum albumin migrates toward the cathode. At hydrogen ion concentrations smaller than  $1.9 \times 10^{-5}$  it migrates toward the anode. When  $(H^+) = 2 \times 10^{-5}$  of a mole per liter, this protein is in an isoelectric condition. The hydrogen ion concentration at which a protein changes the direction of its movement in an electric field is its isoelectric point. The direction of migration of casein changes in the zone between  $1.3 \times 10^{-5}$  and  $4.9 \times 10^{-5}$  of a mole of hydrogen ions per liter. In pure water  $(H^+) = 1 \times 10^{-7}$ .

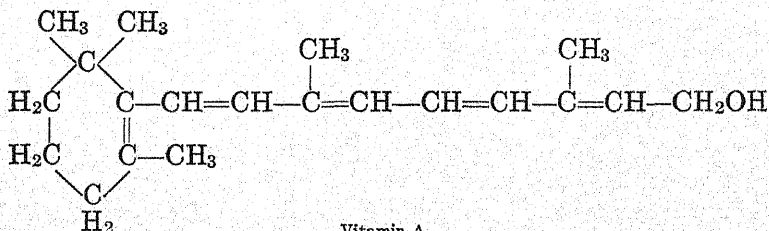
## VITAMINS

The nutritional requirements of man are satisfied by a properly balanced diet composed of proteins, fats, carbohydrates, water, salts, and vitamins. The vitamins are present in extremely small quantities in our foods, but they are as essential as other components of the diet. The mechanism whereby minute traces of specific chemical compounds prevent the development of certain diseases is unknown; but there is no doubt about the realization of such results, and compounds that perform these functions are known as *vitamins*.

**Vitamin A.** Normal growth and the maintenance of good health are dependent upon the presence in the diet of a compound having the empirical formula  $C_{20}H_{30}O$ , known as vitamin A. Cod-liver oil and halibut-liver oil are good sources of this compound. In very small quantities it is found in butter, and in all other fats of animal origin.

A deficiency of vitamin A in the diet retards growth and increases susceptibility to infectious diseases — especially to infectious disorders of the respiratory tract. Lack of this vitamin is associated also with certain disorders of the eye. It is said to be the cause of night blindness, a condition due to an insufficient supply of visual purple in the retina. The early Egyptians recognized night blindness as a pathological condition that could be relieved by the ingestion of liver.

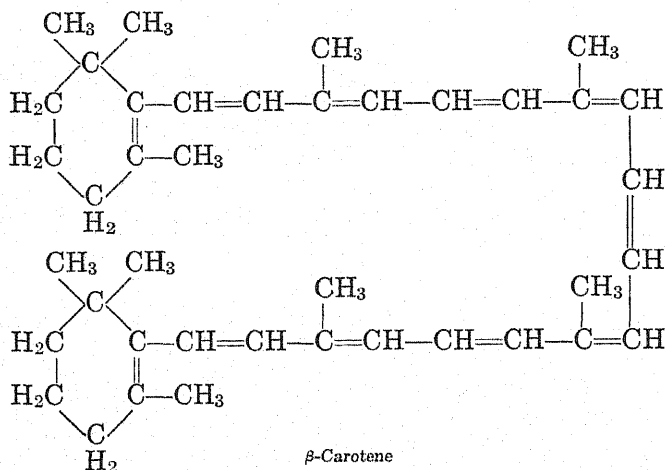
Vitamin A is believed to have the following structure :



Vitamin A

It is closely related to isoprene (see page 30) and to carotene. Carotene,  $C_{40}H_{56}$ , is the pigment that imparts a red or yellow

color to carrots. The growth-promoting activity of vegetables may be due to carotene which, in the process of digestion, yields vitamin A. There are three modifications of carotene known as  $\alpha$ ,  $\beta$ , and  $\gamma$  forms. The formula for  $\beta$ -carotene is shown below :



Lycopin, the red pigment found in tomatoes, is isomeric with carotene ; that is, it has the same empirical formula,  $\text{C}_{40}\text{H}_{56}$ , but a different structure.

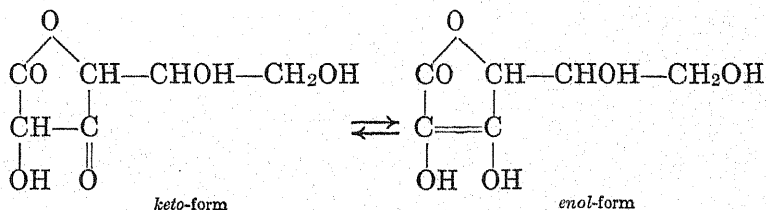
**Vitamin B.** The cause of beriberi, a disease that for many generations took a heavy toll of life in Japan, China, and India, was traced to the use of polished rice as the main foodstuff. The disorder was prevented when whole rice was substituted for the milled product. Well-developed cases of the disease have been cured by the addition of rice bran to the food of the patients. The pericarp, or outer layer, of the rice kernel contains a chemical substance which prevents and cures the disease known as beriberi. The chemical nature of this substance has not been determined. It is present in extremely small quantities in the grain, and attempts to isolate it in a pure state and to determine its chemical constitution have failed.

Vitamin B has been obtained from many sources, including milk, yeast, egg yolk, and all cereals. The active substance has been concentrated and obtained in solid form. Several possible structural formulas for the compound have been written, but the evidence in support of any formula proposed, up to the present time, is inconclusive. With hydrochloric acid the vita-

min forms a crystalline salt which, according to Jansen and Donath, corresponds to the formula  $C_6H_{10}N_2O \cdot HCl$ . The compound fails to react with nitrous acid. We may assume, therefore, that it is neither a primary nor a secondary amine. It is probable that the nitrogen atoms are in a pyrimidine ring or in an imidazole ring.

**Vitamin C.** Scurvy is a disease that develops when there is a deficiency of vitamin C in the diet. This vitamin is present in small but sufficient quantities in most green vegetables, and it is especially abundant in lemons, oranges, and tomatoes. When vitamin C is not present in the diet the bones become brittle, the teeth loosen, and hemorrhages accompany any bone injury. Milk contains the antiscorbutic substance in sufficient quantities to afford protection against scurvy when milk constitutes the complete diet. Pasteurized milk is only slightly inferior to raw milk in this respect.

Vitamin C, known also as ascorbic acid, has the empirical formula  $C_6H_8O_6$ . The compound exhibits keto-enol tautomerism and corresponds to the following structures:

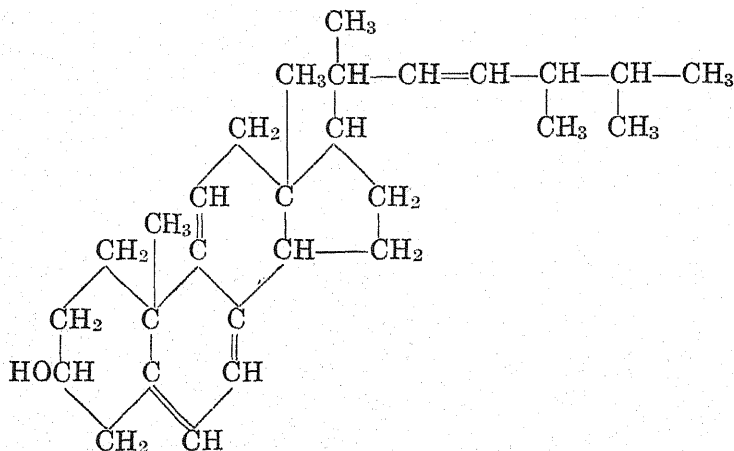


**Vitamin D.** This compound is known as the antirachitic vitamin. In its absence calcium metabolism is imperfect and the bones are not properly nourished. In children lack of this substance causes rickets. As in the case of vitamin A, this substance is found in the fish-liver oils.

Ergosterol,  $C_{28}H_{44}O$ , is a compound that is widely distributed in nature and especially abundant in oils derived from animals. When ergosterol is irradiated with ultra-violet light, vitamin D is formed. Ergosterol and vitamin D have the same empirical formula. The conversion of ergosterol into the vitamin is accomplished through a molecular rearrangement which is catalyzed by light. Light corresponding to a wave length of  $275 \mu\mu$  or longer is advantageously employed. Light of higher frequency (shorter wave length) gradually decomposes the



vitamin.\* The structural formulas of ergosterol and vitamin D have not been definitely established. The following formula for ergosterol has been proposed, but it has not been verified by a synthetic procedure. The formula is in harmony with the facts that, up to the present time, have been established with reference to this compound.



Ergosterol (m.p. 160°)  
(provisional formula)

The isocyclic system of three six-membered rings and one five-membered ring shown in the ergosterol formula is found in many compounds of great importance in the field of biochemistry. All sterols contain this structural nucleus. The sterols found in plants and in animals are colorless crystalline cyclic alcohols of high molecular weights. Cholesterol,  $C_{27}H_{45}OH$ , which is present in human fats and especially in the lipoids of the brain, has a structure very similar to that of ergosterol. Cholesterol is an important component of the blood and of the bile, and it is the principal component of human gallstones. Cholic acid, taurocholic acid, and other bile acids belong also to this group.

**Vitamin E.** A substance known as vitamin E performs an important function in preserving fertility in the animal kingdom. The compound, apparently, is not related to the sex hormone of the pituitary body. Sterility follows the use of a diet from which this vitamin has been excluded. Rats have

\* Reerink and Van Wijk, *Biochem. J.*, **23**, 1294 (1929).

been used in experiments of this kind.\* Although the compound is known as the *antisterility* vitamin, it is no more important, in the matter of maintaining fertility, than is vitamin A. The absence of vitamin A stops reproduction. The importance of vitamin E seems to be limited to its role in promoting fertility, whereas vitamin A performs many other functions. Vitamin E is found in many vegetables, especially in lettuce. Wheat-germ oil and fish oils are other prolific sources.

For a critical review of the literature relating to these compounds see *The Vitamins*, Sherman and Smith, Reinhold Publishing Corporation, New York.

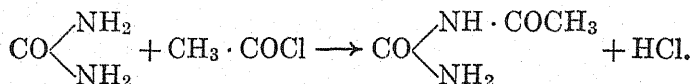
\* Evans and Burr, *J. Am. Med. Assn.*, **88**, 1462 (1927).

## PURINES AND PYRIMIDINES

### THE PURINES

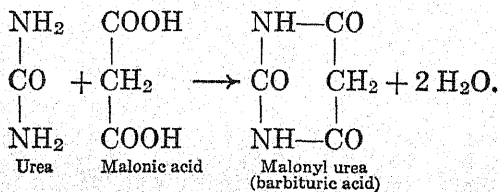
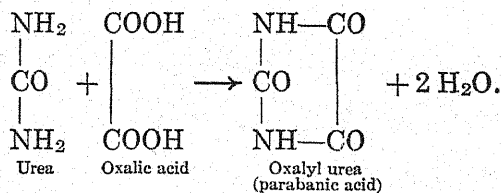
In order to establish structural formulas for purine and its derivatives we must first become acquainted with a few simple condensation products of urea.

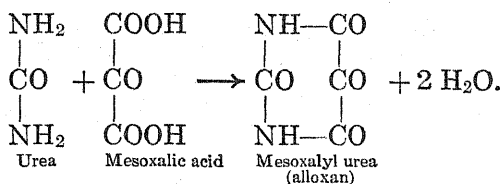
Urea is an amide of carbonic acid. Retaining to some extent the character of ammonia, it reacts with acid chlorides, forming substituted amides. Thus, for example, it combines with acetyl chloride, forming acetyl urea :



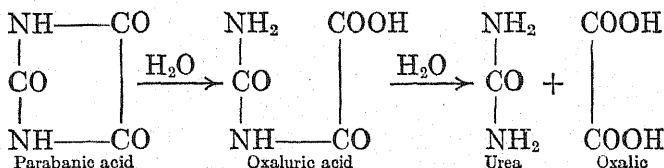
Acetyl urea crystallizes in long, silky needles, melting at 214°. When boiled with an alkali it is hydrolyzed to acetic acid, carbon dioxide, and ammonia.

Similar products are formed with urea and dibasic acids. The reaction is usually carried out by heating a mixture of the acid and urea with phosphorus oxychloride,  $\text{POCl}_3$ , at temperatures ranging from 100° to 200° :



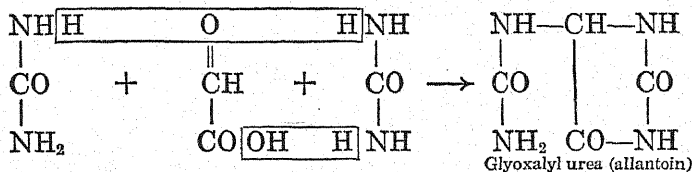


These cyclic compounds are crystalline solids. They are all readily decomposed by boiling them with alkali, the hydrolysis occurring in two stages. Oxalyl urea, commonly called parabanic acid, reacts with one molecule of water to yield oxaluric acid. By continuation of the hydrolysis an additional molecule of water is used, urea is liberated, and oxalic acid is formed. (Salts rather than free acids are the actual products, for the hydrolysis is accomplished in alkaline solution.)

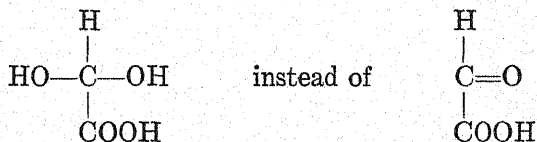


As a final step the urea is hydrolyzed to carbon dioxide and ammonia. All amides are hydrolyzed by hot alkalis.

Two molecules of urea combine with one of glyoxalic acid to form allantoin. The condensation may be written as follows:



Glyoxalic acid is always associated with one molecule of water, and although it has the properties of an aldehyde it may have the structure

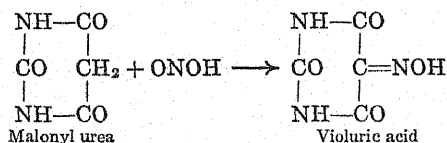


It is one of the few compounds in which two hydroxyl groups seem to be held by the same carbon atom.

Allantoin is a tasteless, odorless, crystalline substance, which melts and decomposes at 231°. It forms insoluble salts of lead, silver, copper, and mercury. It is soluble in water and in alcohol, and is hydrolyzed by hot alkalies to carbon dioxide, ammonia, and a salt of glyoxalic acid.

The hydrogen atoms in the malonic acid residue of malonyl urea are replaceable by metals or by halogens, as they are in malonic ester. Thus, by the action of sodium and subsequent treatment with an alkyl halide, any mono-alkyl or di-alkyl derivative of barbituric acid may be prepared.

Malonyl urea reacts with nitrous acid, yielding violuric acid, and hydroxylamine acts upon mesoxalyl urea to form the same compound. The structure of violuric acid is consequently established:



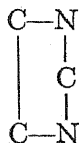
Violuric acid is a colorless, crystalline solid. Its esters are colorless also; but it forms yellow, red, and blue salts. The structures of these salts have not been determined with certainty.

*Uric acid* occurs in small quantities in the blood and in normal urine. It is present in large amounts in guano (18 per cent to 25 per cent) and is the chief component of the excrement of serpents. It is crystalline, odorless, and tasteless, very slightly soluble in water (1 : 10,000), and insoluble in alcohol and ether. Even the alkali metal salts of uric acid are only sparingly soluble. The monosodium salt dissolves in 1100 times its weight of water at 15°; the corresponding lithium salt dissolves in 370 parts of water. The disodium salt of uric acid is much more soluble (1 : 60).

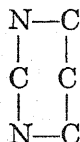
The history of the researches that led to the proof of the structure of uric acid is fascinating and instructive. Only an outline of the problem can be given here. The first serious attempt to determine the chemical nature of uric acid was made by Baeyer in 1863. The accepted formula was proposed by Medicus in 1875, and its validity was proved by Fischer in 1883. The main reactions that were used in establishing the structure of the uric acid molecule were oxidation processes that broke the molecule into simple units, each of which could be identified and synthesized.

From the results obtained by analyses and molecular-weight determinations, its molecular formula is shown to be  $C_5H_4N_4O_3$ .

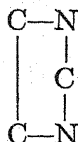
When oxidized by potassium permanganate in alkaline solution, uric acid yields allantoin. It therefore contains two urea residues and the ring structure found in allantoin:



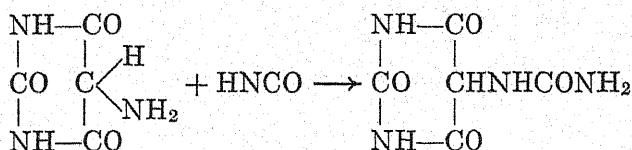
When oxidized with nitric acid, uric acid yields alloxan and parabanic acid. It therefore possesses a structure that includes the rings found in these compounds, namely:



and

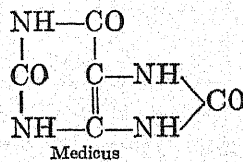
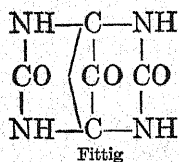
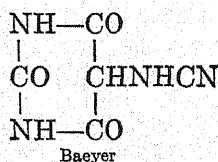


By condensing cyanic acid with uramil, Baeyer synthesized a compound which he called pseudo-uric acid. It differs from uric acid by one molecule of water:



He tried in vain to dehydrate this compound in such a way as to leave uric acid. Fischer completed Baeyer's task by dehydrating pseudo-uric acid through the agency of hot hydrochloric acid. Uric acid was thus produced synthetically.

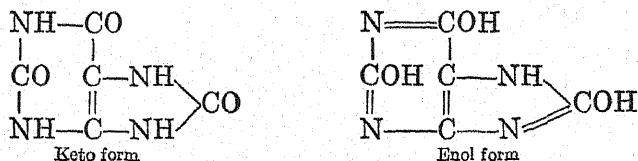
On the basis of these facts, Baeyer, Fittig, and Medicus proposed the following structures for the uric acid molecule:



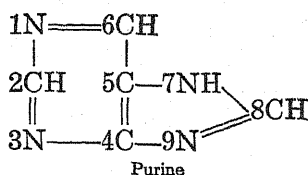
Fischer proved the presence of four imide groups in uric acid by preparing a tetramethyl derivative, from which all the

nitrogen in the compound could be obtained, by saponification, in the form of methylamine. This evidence was in harmony with the formulas proposed by Medicus and Fittig, but it ruled out the Baeyer structure. Hill, at Harvard, made the next advance by preparing two different monomethyl derivatives, in each of which the methyl group was attached to nitrogen. The symmetrical formula of Fittig, therefore, had to be rejected. Finally Fischer confirmed the Medicus formula by showing that on oxidation one of Hill's monomethyl derivatives yields alloxan and methyl urea, whereas the other, under similar treatment, yields methyl alloxan and urea. In other words, only one of the two imide (NH) groups in which the methyl radical had been substituted for the hydrogen atom was in the alloxan ring.

In many of its reactions uric acid acts as if its oxygen atoms were in hydroxyl groups. Phosphorus trichloride, for example, acts upon uric acid, forming trichloropurine. In this reaction three oxygen and three hydrogen atoms are replaced by three chlorine atoms. In some other reactions uric acid behaves like a ketone. It is a phenomenon similar to that displayed by the oximes and acetoacetic ester. It is a case of keto-enol tautomerism, and the two structures of uric acid correspond to the formulas

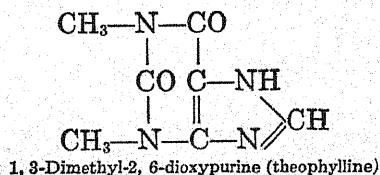
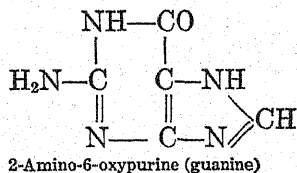
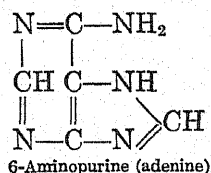
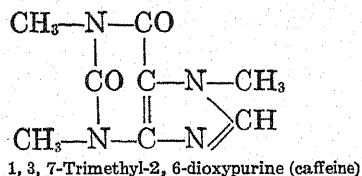
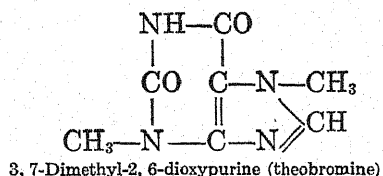
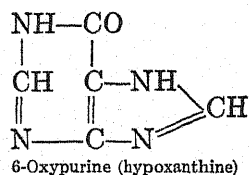
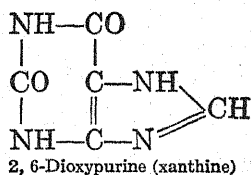
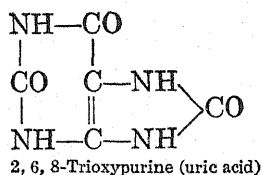
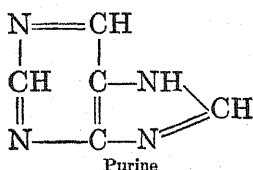


*Purine.* A colorless, crystalline compound composed of carbon, hydrogen, and nitrogen only, and having the same condensed carbon and nitrogen rings as found in uric acid is known as purine. Its structure was written and the name applied to it fourteen years before the compound was known to exist. It was, therefore, at first a purely hypothetical substance representing what might be expected to form if uric acid could be reduced until it contained only the three elements mentioned, without changing the ring structure. Uric acid and all other compounds having the same carbon-nitrogen skeleton are regarded as purine derivatives and named in accordance with the positions occupied by substituting groups. The positions of the elements in the purine rings are numbered as follows:



Purine is a very weak base. It melts at  $217^\circ$  and dissolves readily in water. All its oxy-derivatives display keto-enol tautomerism.

The systematic names and the common names and formulas of some purine derivatives are shown below :





*Caffeine* crystallizes from water in white needles having a silky luster and a bitter taste. It sublimes under atmospheric pressure at  $178^{\circ}$ , and melts in a sealed tube at  $237^{\circ}$ . Caffeine occurs in coffee (0.5 per cent to 1.5 per cent). Its physiological action is of some importance. It acts (1) upon the central nervous system, (2) upon the kidneys, and (3) upon the heart. It is a cerebral stimulant. It overcomes drowsiness and relieves fatigue. Intravenously injected it quickens the heart action and temporarily produces a stronger pulse. Upon the kidneys it acts as a diuretic, and on this account its use has been advocated in the treatment of various types of oedema. In addition to these chief characteristics one other effect should be mentioned which, however, is not general but depends largely upon the idiosyncrasies of individuals, namely, its influence upon digestion. Many suffer from indigestion if caffeine is used in large amounts.

*Theobromine* is found in chocolate (1 per cent to 2 per cent). It is a colorless, crystalline body which sublimes at  $290^{\circ}$  (m.p.  $337^{\circ}$ ). Like caffeine it is a nerve stimulant and a diuretic. It is only slightly soluble in water and in alcohol but dissolves readily in ether. Theobromine, caffeine, and other purines are partly oxidized in passing through the body and are excreted chiefly in the form of uric acid.

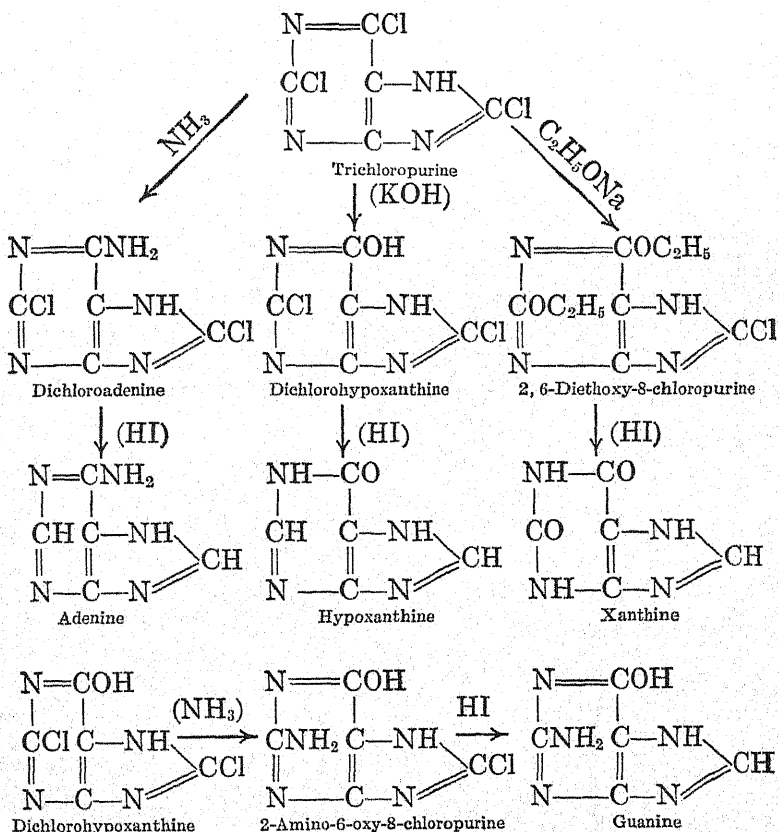
*Adenine* is obtained as a hydrolysis product of nucleoproteins of both plant and animal origin, and may be obtained in crystalline form from an aqueous extract of tea leaves. It decomposes at  $365^{\circ}$ .

*Guanine* occurs with adenine in plant and animal tissues and especially in nucleic acid. It is practically insoluble in water and in alcohol, but dissolves in basic solutions. Guanine and adenine are the only amino purines found in nature.

*Trichloropurine* is prepared by treating uric acid with phosphorus oxychloride; and from this derivative most of the purine bases may be made by direct processes of substitution. The control of these substitutions is rendered possible by the fact that the chlorine in position 6 is far more reactive than either of the others, and the halogen atom in position 2 is more reactive than the one in position 8. Thus, when 2, 6, 8-trichloropurine is warmed with hydriodic acid, only chlorine 6 is replaced by hydrogen. Chlorine atoms 2 and 8 are, at the

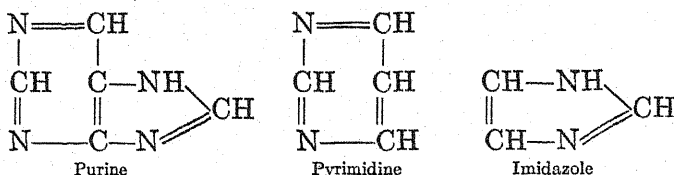
same time, replaced by iodine. The di-iodopurine may be completely reduced by heating with zinc dust and water, and in this way purine was synthesized.

Ammonia acts upon trichloropurine, replacing the chlorine at position 6 by  $\text{NH}_2$ . Potassium hydroxide replaces the same chlorine by a hydroxyl group. Sodium alcoholate replaces chlorine atoms 2 and 6 by alkoxyl groups; and in any of these derivatives the remaining chlorine may be replaced by hydrogen through reduction with hydriodic acid and zinc. The principal reactions involved in the conversion of trichloropurine into other derivatives of purine are summarized in the following table:

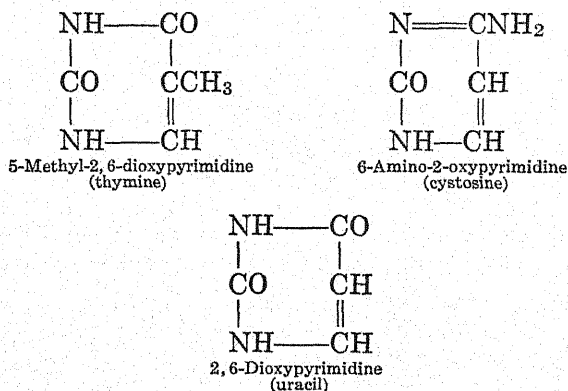


## THE PYRIMIDINES

The purine molecule contains a six-membered ring and a five-membered ring. The two are merged so that two of the carbon atoms belong to both rings. The separate rings, with hydrogen enough to satisfy the carbon valences, represent two definite compounds, known as pyrimidine and imidazole:

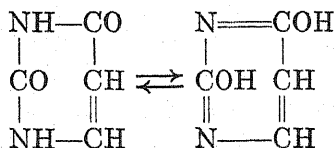


The atoms of the pyrimidine ring are numbered just as they are in purine, and derivatives of this cyclic structure are named as substituted pyrimidines. As a result of the exhaustive researches of Treat B. Johnson, the reactions of the pyrimidines and methods for synthesizing them are well known. Some of these derivatives are important components of every living cell. The nucleoproteins, for example, are composed of simple proteins, combined with a substance of unknown structure called nucleic acid; and nucleic acid when hydrolyzed yields phosphoric acid, carbohydrates, purines, and pyrimidines. Among the more important members of the last class are thymine, cystosine, and uracil:



These derivatives of pyrimidine are not very soluble in water. They decompose at their melting points: thymine, 321°;

cystosine, 324°; and uracil, 338°. On treatment with nitrous acid cystosine is converted into uracil. It is the usual replacement of an amino group by a hydroxyl group. In the same way adenine is converted into hypoxanthine and guanine into xanthine. Uracil and other oxypyrimidines, and the oxypurines as well, exist in two forms, corresponding to keto and enol structures. In solution an equilibrium is established between the two forms. If a reagent is used which reacts with a carbonyl oxygen, any one of these tautomeric compounds will behave as if it were a ketone. With a reagent which acts on a hydroxyl group the same compound responds with equal ease in the enolic form. Uracil in solution has the following structures :



## THE ALKALOIDS

The term *alkaloid* has been applied to any basic substance of vegetable origin which contains nitrogen in a heterocyclic ring. This definition of the term is too broad. It brings into the alkaloid group many compounds that, from a chemical point of view, are in no way related to each other. But attempts to classify the alkaloids on the basis of structure have been unsuccessful, and, with some reservations, this vague definition is still used. It is doubtful whether the purine bodies, caffeine, theobromine, and related substances, should be called alkaloids, yet they are plant products sufficiently basic to form salts with strong acids, and they have nitrogen-carbon ring structures.

Most of the typical alkaloids are derivatives of pyridine or quinoline, but to define them as such derivatives would exclude morphine, the most important member of the group, the first one isolated, and the one to which the name was first applied.

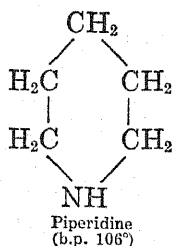
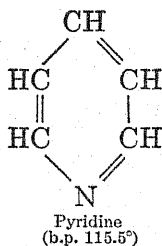
More than two hundred vegetable bases have been isolated, analyzed, and described. The structures of many of them have been determined, and some of them have been produced synthetically. An acquaintance with pyridine, pyrrole, quinoline, isoquinoline, and some of their derivatives is a prerequisite to the study of the alkaloids.

*Pyridine*,  $C_5H_5N$ , is a colorless liquid, possessing a persistent and disagreeable odor. It dissolves in all proportions in water, alcohol, and ether. It is obtained from bones by dry distillation, from coal tar, and from crude petroleum. It is obtained from nicotine and from quinine when these alkaloids are heated with zinc dust. It is reduced to piperidine by treatment with sodium amalgam and water. At a high temperature it reacts with hydrogen iodide, yielding normal pentane and ammonium iodide.

Pyridine is a very stable compound. Oxidizing agents such as chromic acid, potassium permanganate, and concentrated

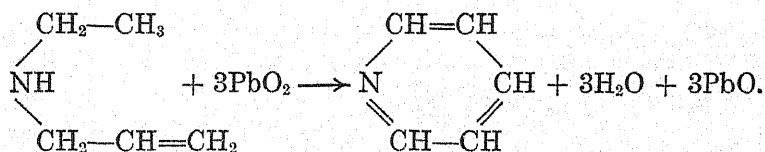
nitric acid do not attack it. At 300° concentrated sulfuric acid acts upon it slowly, forming a  $\beta$ -monosulfonic acid.

The structure of pyridine corresponds to benzene in which one CH group has been replaced by nitrogen. It exhibits the same state of unsaturation as does benzene. The reduction product, piperidine, referred to above, is a saturated cyclic compound.

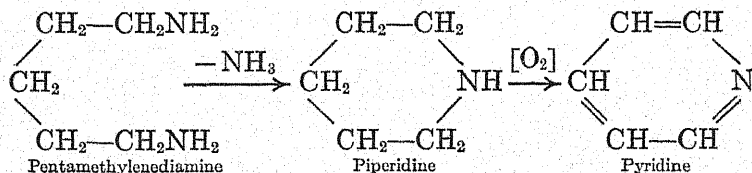


Pyridine may be prepared by the following methods :

1. Ethylallylamine is oxidized by lead dioxide at 450°.

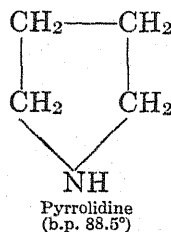
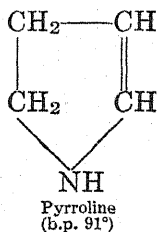
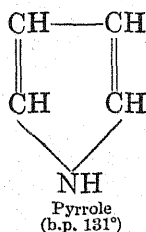


2. Pentamethylenediamine, when heated, yields ammonia and piperidine. The latter is oxidized to pyridine by heating it with nitrobenzene.



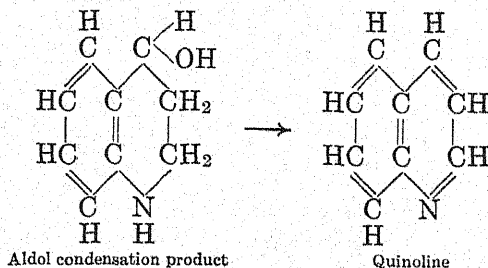
*Pyrrole*,  $\text{C}_4\text{H}_5\text{N}$ , is a component of bone oil. It is separated from pyridine by treatment with sulfuric acid. Pyrrole is not sufficiently basic to form a salt with the acid. On the other hand, it is sufficiently acidic to form a potassium salt when warmed with the free metal. The salt is hydrolyzed extensively when dissolved in water. Zinc and acetic acid reduce pyrrole

to pyrroline. Sodium and alcohol convert the latter into a basic substance called pyrrolidine.



*Quinoline* (b.p. 237.7°) is a colorless, hygroscopic liquid. Like pyridine and other tertiary amines it forms quaternary salts by addition of alkyl halides or halogen acids. It bears the same relation to naphthalene that pyridine does to benzene. Skraup synthesized quinoline by heating a mixture of aniline, glycerine, sulfuric acid, and nitrobenzene. The glycerine is dehydrated by sulfuric acid, and acrolein,  $\text{CH}_2=\text{CH}-\text{CHO}$ , is formed. Aniline and acrolein yield a condensation product which is oxidized to quinoline by nitrobenzene.\*

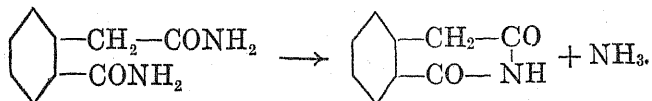
The formation of quinoline is probably accomplished by the following series of reactions: Acrolein has conjugated double bonds,† and aniline acts upon it, forming a 1, 4 addition product,  $\text{C}_6\text{H}_5-\text{NH}-\text{CH}_2-\text{CH}=\text{CHOH}$ . This unstable intermediate product immediately assumes the isomeric form,  $\text{C}_6\text{H}_5-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CHO}$ . By an aldol type of condensation (hydrogen passing from the *ortho* position in the benzene ring to the carbonyl oxygen in the side chain) a heterocyclic ring is formed. This product is oxidized and dehydrated, with the formation of quinoline:



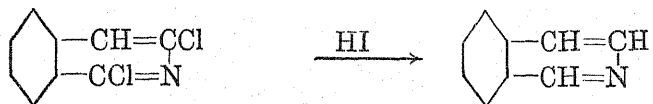
\* For a list of possible products formed from nitrobenzene when it is heated with a reducing agent, see page 213.

† See Conjugation and Resonance, page 385.

*Isoquinoline* is isomeric with quinoline and has very similar properties. Structurally it differs from quinoline only in the position of the nitrogen atom. It has been synthesized by heating the amide of phenylacetic-*o*-carboxylic acid and reducing the resulting imide:

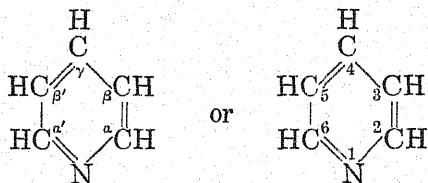


This imide enolizes in the presence of phosphorus oxychloride and is converted into dichloroisoquinoline. Hydrogen iodide reduces the latter to isoquinoline:

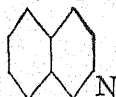


Many other methods have been devised for synthesizing pyridine, quinoline, and isoquinoline.

The presence of nitrogen in the ring makes the possible number of isomeric substituted pyridines much greater than the number of corresponding benzene derivatives. There are three monosubstitution products and six disubstitution products of pyridine. The positions in the ring are indicated by the letters of the Greek alphabet or by numbers:



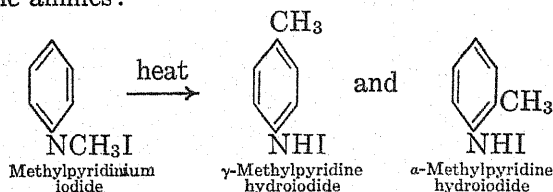
For economy of space, the formulas of pyridine, quinoline, and isoquinoline may be written as follows:



It must be remembered, however, that in each case the nitrogen atom is in the ring and not externally attached to the ring.

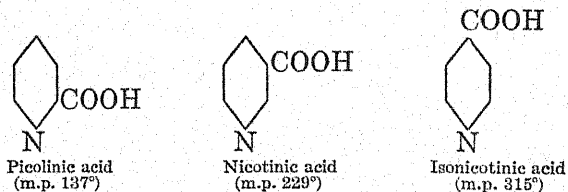


Quaternary salts of pyridine are formed by direct addition of alkyl halides. When heated to 300°, these compounds undergo rearrangement corresponding to the shift of alkyl radicals from nitrogen to carbon in salts of aniline and of other aromatic amines:

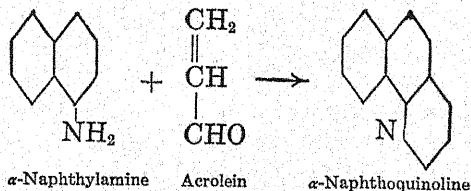


Free  $\alpha$ - and  $\gamma$ -methylpyridine are obtained by distilling alkaline solutions of the corresponding hydroiodides.

Three monocarboxylic acids of pyridine are known, and according to the structure theory only three are possible. They are produced when certain alkaloids are subjected to oxidation, or they may be synthesized by oxidizing the  $\alpha$ -,  $\beta$ -, and  $\gamma$ -alkyl derivatives of pyridine. These acids are colorless crystalline compounds. They are represented by the following formulas:

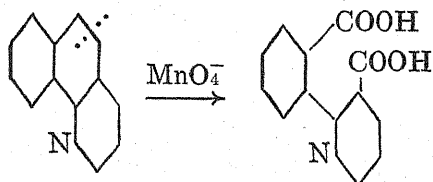


The structures of these acids have been proved by synthetic methods. For example, applying the principle of Skraup's synthesis of quinoline, we may condense  $\alpha$ -naphthylamine with acrolein in the presence of a mild oxidizing agent, such as nitrobenzene, and obtain  $\alpha$ -naphthoquinoline.

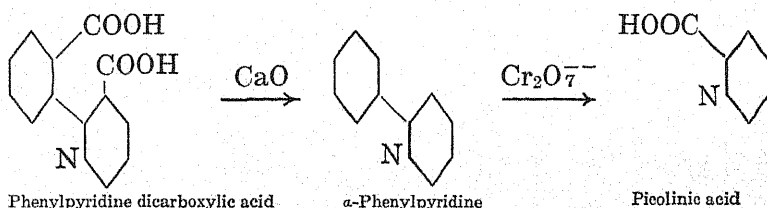


By oxidation it is possible to convert this product into a dicarboxylic acid without loss of carbon. There is only one position

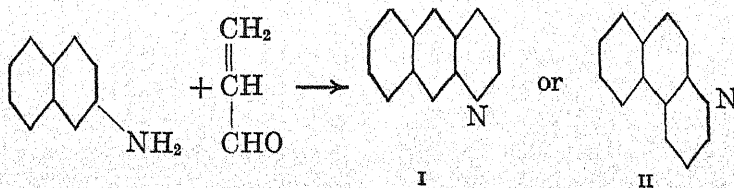
in the molecule where, by oxidation, two carboxyl groups could be formed without producing an acid with fewer carbon atoms. The position is indicated by the dotted line below :



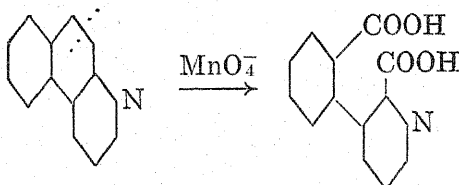
The carboxyl groups are replaced by hydrogen when the acid is distilled with lime, and the resulting  $\alpha$ -phenylpyridine is converted by chromic acid into picolinic acid:



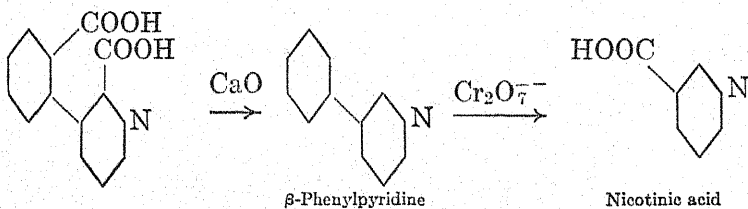
The constitution of nicotinic acid may be determined in a similar way. Acrolein combines with  $\beta$ -naphthylamine as it does with aniline or  $\alpha$ -naphthylamine. The condensation product is oxidized by nitrobenzene, forming a pyridine ring by attachment of the terminal carbon atom of the acrolein residue to a carbon atom *ortho* to the nitrogen of the aromatic amine. In Skraup's synthesis of quinoline it makes no difference which of the two positions *ortho* to the amino group is involved in the formation of the pyridine ring. When acrolein is condensed with  $\alpha$ -naphthylamine, as in the case referred to in the synthesis of picolinic acid, only one position *ortho* to the amino group is available.  $\beta$ -Naphthylamine presents two possibilities:



The product actually formed can be converted into a dicarboxylic acid without loss of carbon. There is no possibility of oxidizing formula I so as to produce a dicarboxylic acid, without at the same time reducing the number of carbon atoms in the molecule, and formula II presents only one such possibility, as indicated below:



The carboxyl groups are removed by distillation with lime, and the remaining phenyl radical is replaced by carboxyl through the agency of chromic acid. The superior stability of the pyridine ring is shown in these reactions. It is the benzene residue that suffers oxidation, yielding in this case nicotinic acid rather than benzoic acid:

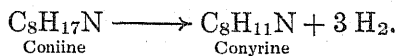


### CONIINE

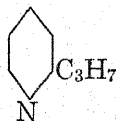
Coniine,  $\text{C}_8\text{H}_{17}\text{N}$ , a colorless liquid (b.p.  $166^\circ$ , sp. gr. 0.845), is the principal alkaloid in hemlock. The poisonous character of an extract of hemlock was known before the dawn of the Christian era. The fatal dose is from 0.1 to 0.2 of a gram. There is no satisfactory antidote.

The free base was isolated by Geiger in 1831, and synthesized by Ladenburg fifty years later. It was the first alkaloid to be made by artificial methods. The constitution of the compound was determined by Hofmann through an interpretation of the following changes.

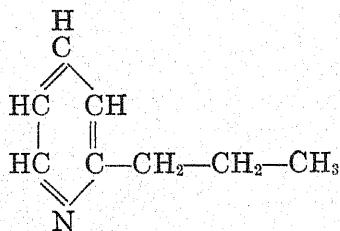
When coniine is distilled over zinc dust, it gives rise to free hydrogen and a compound known as conyryne, having the empirical formula  $C_8H_{11}N$ .



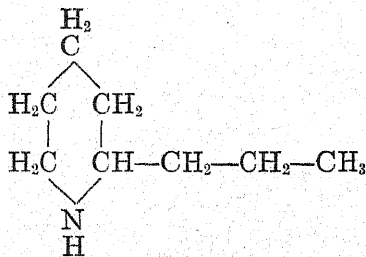
Conyryne is readily oxidized to picolinic acid, which differs from conyryne by  $C_2H_6O_2$ . The two oxygen atoms are introduced by the oxidizing agent in forming the carboxyl group, — conyryne itself contains no oxygen. The loss of carbon and hydrogen in the oxidation process amounts, therefore, to  $C_2H_6$ . Since picolinic acid has only one carboxyl group, it is evident that conyryne is a derivative of pyridine with one and only one side chain. The side chain must be in the  $\alpha$  position, since in picolinic acid the carboxyl group occupies this position. The composition of the side chain must be  $C_3H_7$ . It is  $C_2H_6$  plus the carbon and hydrogen retained in the carboxyl group. The formula may be written



The question as to whether the side chain is normal propyl or isopropyl was settled by subjecting conyryne to the action of hydriodic acid at  $300^\circ C$ . It was reduced to normal octane and ammonia. Conyryne is, therefore, normal propylpyridine, and coniine, having six more hydrogen atoms, is the corresponding saturated compound, *n*-propylpiperidine:



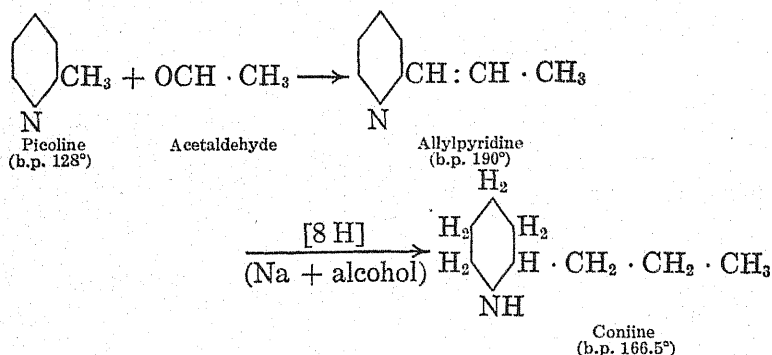
Conyryne



Coniine

All syntheses of coniine lend support to the conclusion that it has this structure. The simplest and most direct synthesis is accomplished by condensing  $\alpha$ -methylpyridine (picoline) with

acetaldehyde, in the presence of zinc chloride, and reducing the condensation product:



The racemic mixture produced by this synthesis was resolved by Ladenburg into the optically active forms, by fractional distillation of the coniine tartrates. The dextrorotatory modification and coniine derived from hemlock were found to be identical.

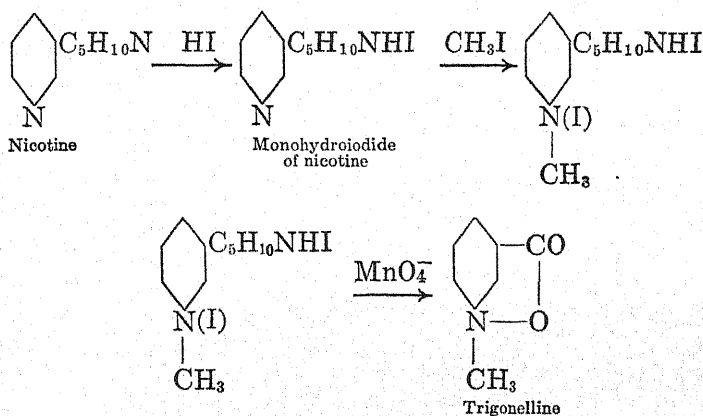
### NICOTINE

Nicotine,  $C_{10}H_{14}N_2$ , when pure, is a colorless, odorless liquid. It acquires a brown color and a tobacco odor on standing. It is fully as poisonous as hydrocyanic acid and about ten times as poisonous as coniine. It has an alkaline reaction, produces a burning sensation in the mouth, and causes profuse salivation. Acute nicotine poisoning gives rise to mental confusion, vomiting, and finally convulsions.

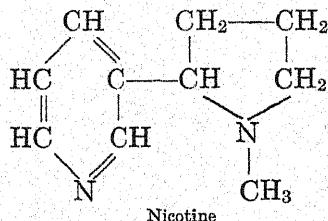
Nicotine occurs in the leaves of the tobacco plant, principally in the form of salts of malic and citric acids. The tobacco plant is the chief source of this alkaloid. The plant is indigenous to America and was unknown in Europe until 1650. The component of tobacco that acts as a habit-forming drug has not been discovered. It is not nicotine.

Nitric acid converts nicotine into nicotinic acid. The alkaloid is therefore a pyridine derivative, and the side chain,  $C_5H_{10}N$ , is in the  $\beta$  position. Nicotine is a ditertiary base, yielding, with methyl iodide, two different quaternary salts. Each nitrogen atom, therefore, is linked by three valences to carbon. The nitrogen of the pyridine ring is less basic than the

one in the  $C_5H_{10}N$  group; for when the monohydroiodide is treated with methyl iodide and then oxidized with potassium permanganate, trigonelline is formed — a compound known to have a methyl group on the pyridine nitrogen. In forming the monohydroiodide it is evident that the hydrogen iodide enters into combination with the nitrogen of the  $C_5H_{10}N$  group, leaving the nitrogen of the pyridine ring free. On further treatment with methyl iodide or hydrogen iodide the pyridine nitrogen also is called into play:



The monohydroiodide when heated yields methylamine. The group  $C_5H_{10}N$  must, therefore, contain a methyl group attached to the nitrogen. On the basis of these and other considerations, the following structure is assigned to nicotine:



Pictet confirmed this constitution of the alkaloid by synthesizing  $\beta$ -methylpyrrolidinepyridine and resolving it into its enantiomorphic forms. The laevorotatory compound proved to be nicotine.

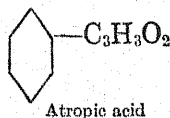
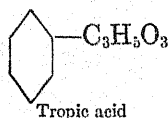
## ATROPINE

Atropine,  $C_{17}H_{23}NO_3$ , a colorless, crystalline alkaloid, is obtained from the roots and leaves of the nightshade by extraction with alcohol. Distinct symptoms of poisoning follow the ingestion of quantities as small as 0.006 of a gram of atropine, and 0.05 of a gram constitutes a fatal dose.

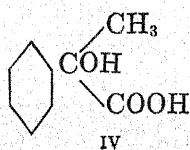
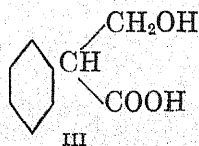
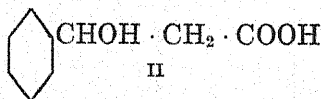
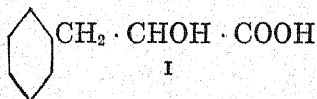
The symptoms are extreme thirst, inability to swallow, hoarseness, and headache. The pupils of the eyes are enlarged, and vision is indistinct. In the last stages violent types of delirium and convulsions are common. Respiration is arrested during the spasms, and in many cases death has resulted from asphyxia. Atropine is used in optic surgery. It acts as a local anæsthetic on the nerves controlling the muscles of the eye.

Atropine is an ester. When hydrolyzed it yields tropic acid and tropine. In order to establish the constitutional formula of atropine it is necessary to determine the structures of these hydrolysis products.

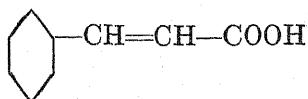
Tropic acid has the empirical formula  $C_9H_{10}O_3$ . Atropic acid is  $C_9H_8O_2$ . Both are converted into benzoic acid by oxidation. Each may, therefore, be represented by a benzene ring with one side chain.



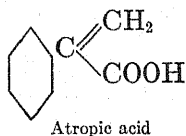
They are monobasic acids, hence each has a carboxyl group in the side chain. Tropic acid has a hydroxyl group also, for it forms an acetyl derivative with acetic anhydride. There are four possible structures for a benzene ring with one side chain — the side chain having the composition  $C_3H_5O_3$  and possessing one carboxyl group and one alcoholic hydroxyl group. One of these structures must represent the tropic acid molecule :



When tropic acid is heated, it loses water and forms atropic acid. Atropic acid has no alcoholic hydroxyl group. It is unsaturated and forms an addition product with bromine. Formulas I and II would yield the same product if water were eliminated and a double bond established with removal of the alcoholic hydroxyl group. Its formula would necessarily be

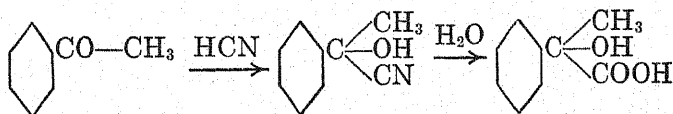


but this is cinnamic acid, not atropic. Therefore tropic acid is not represented by I nor by II. Formulas III and IV would yield the same product if dehydrated, namely,

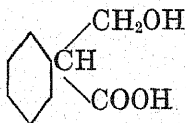


This product is, therefore, atropic acid, and tropic acid is either III or IV.

A compound having formula IV has been made synthetically from acetophenone by the following reactions:



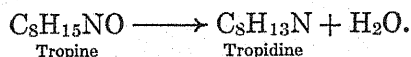
This product is not tropic acid; it is known as atrolactic acid. Formula IV is thus excluded, and the only possible structure for tropic acid is



Tropine,  $\text{C}_8\text{H}_{15}\text{NO}$ , crystallizes in colorless plates (m.p.  $63^\circ$ , b.p.  $233^\circ$ ). It is a strong tertiary base, hygroscopic, and optically inactive. It forms esters with acids and with acid chlorides; hence its oxygen atom is in a hydroxyl group. When distilled with barium oxide, it yields water, methylamine, and tropilidene ( $\text{C}_7\text{H}_8$ ). The latter is a seven-membered ring compound. The production of methylamine indicates that in



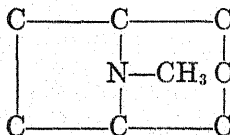
tropine there is a methyl group attached to the nitrogen atom; and since it is a tertiary amine, the nitrogen must be attached to carbon by two other bonds also. When heated to  $220^{\circ}$  with sulfuric acid, tropine yields an unsaturated tertiary base, tropidine, containing no oxygen:



Tropidine is reduced by hot hydriodic acid to normal heptane and methylamine, indicating its possession of a structure capable of yielding an unbranched chain of seven carbon atoms when the nitrogen and its attached methyl group are removed.

Methylpiperidine and methylpyrrolidine have been identified among the products obtained from tropine by distillation with zinc dust. We have, therefore, in tropine a continuous chain of seven carbon atoms and a nitrogen atom attached to a methyl group and to two other carbon atoms. The nitrogen atom is a member of a piperidine ring and at the same time a member of a pyrrolidine ring.

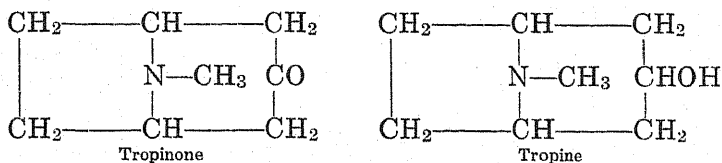
The skeleton of the tropine molecule must, therefore, appear as follows:



When tropine is oxidized with potassium permanganate or lead dioxide, a ketone, tropinone, is formed, differing from tropine by two hydrogen atoms. The hydroxyl group in tropine is therefore in a secondary alcohol group,  $\text{CHOH}$ , and this group is in the six-membered ring; for when the hydroxyl group is replaced by bromine and the compound is decomposed by heat, bromomethylpyridine is formed. Similar evidence is obtained by dehydrating tropine by means of hot sulfuric acid. The hydroxyl group is removed with hydrogen from an adjacent carbon atom. The unsaturated product formed (namely, tropidine,  $\text{C}_8\text{H}_{13}\text{N}$ ) absorbs bromine, yielding tropidine dibromide,  $\text{C}_8\text{H}_{13}\text{NBr}_2$ , which decomposes at  $180^{\circ}$ , with the formation of dibromomethylpyridine.

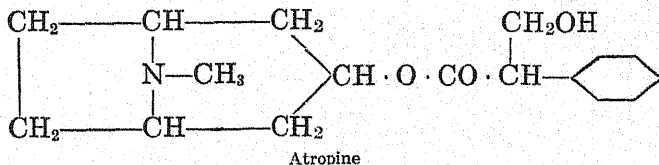
Conversion of a secondary alcohol into a ketone enhances the activity of hydrogen on carbon atoms adjacent to the oxidized group. Consideration of this fact led Willstätter to the

conclusion that the carbonyl group in tropinone is between two methylene ( $\text{CH}_2$ ) groups, for tropinone reacts with nitrous acid, yielding a di-isonitroso derivative, and with benzaldehyde, giving a dibenzal derivative. Tropine is the corresponding secondary alcohol. The following structures account for the properties of these compounds:

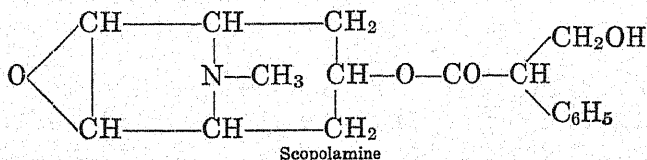


Tropine has a ring system including piperidine, pyrrolidine, and heptamethylene nuclei. The structure accounts for the formation of methylamine and heptane on reduction, the production of pyridine derivatives when oxidized with bromine, the formation of tropidine by elimination of water, and all other properties of the base.

Atropine is the tropine ester of tropic acid,



Scopolamine (hyoscyne),  $C_{17}H_{21}NO_4$ , is another alkaloid belonging to this group. It is represented by the following formula:

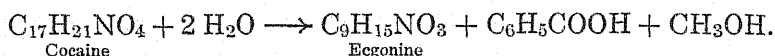


# COCAINE

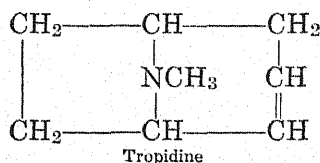
Cocaine,  $C_{17}H_{21}NO_4$ , is a white crystalline solid melting at  $98^\circ$ . It is extracted from coca leaves. It has a bitter taste, an alkaline reaction, and is laevorotatory. It has been used extensively as a local anæsthetic, but it is being supplanted by the less harmful novocaine — a synthetic product not related

to the alkaloids. Cocaine is a poison, but it requires a large dose (nearly one gram) to cause death in man. Small doses cause restlessness and irritability, with quickened pulse. It is used habitually in very small amounts by some individuals who claim that it acts as a tonic, overcoming fatigue and sensations of hunger. Many workmen in the Andes chew the coca leaves, believing that they derive therefrom unusual power of endurance.

On hydrolysis cocaine yields ecgonine, benzoic acid, and methyl alcohol:



Ecgonine is a monobasic acid and a monohydric alcohol. When warmed with sulfuric acid it yields water and anhydroecgonine,  $\text{C}_9\text{H}_{13}\text{NO}_2$ . The latter is an unsaturated acid. It retains the carboxyl group of ecgonine, but it has no alcoholic properties. At  $280^\circ$  anhydroecgonine decomposes, yielding tropidine and carbon dioxide. It will be recalled that tropidine is formed when a molecule of water is removed from tropine; its structure, therefore, is known:

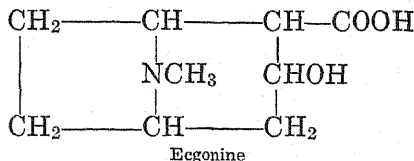


It is obvious, from the reactions mentioned above, that anhydroecgonine is tropidine carboxylic acid, but the position of the carboxyl group must be determined.

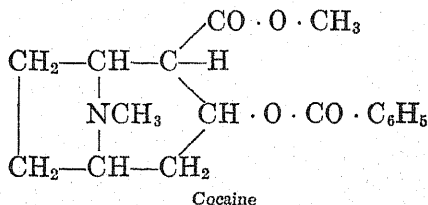
The hydroxyl group in ecgonine occupies the same position that it does in tropine, for the removal of the carboxyl group in ecgonine (and simultaneous oxidation of the  $\text{CHOH}$  group to carbonyl) by treatment with dilute chromic acid solution results in the formation of tropinone.

Anhydroecgonine can be reduced to a saturated carboxylic acid. The carboxyl group may then be replaced by an amino group by converting the acid to an amide and warming the amide with bromine and potassium hydroxide (Hofmann rearrangement). When the amino group is replaced by a hydroxyl group through the agency of nitrous acid, the product

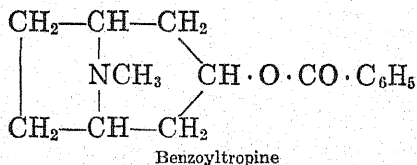
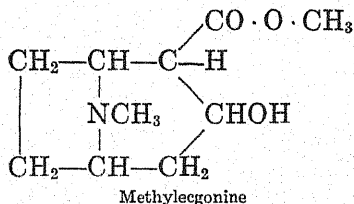
obtained is an isomer of tropine and identical with one of the products obtained from tropidine by the addition of hydrogen bromide and subsequent hydrolysis of the bromine derivative. Hence in ecgonine the hydroxyl group and the carboxyl group are on adjacent carbon atoms:



Cocaine, therefore, corresponds to the following structure:

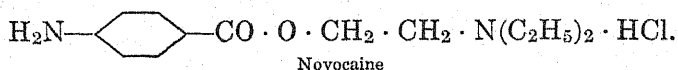


The effects produced upon the sensory nerves by this alkaloid have been traced to the reciprocal relations of the tropine, benzoyl, and methoxy groups. Methylecgonine and benzoyltropine do not resemble cocaine in physiological properties.



With both ester groups in the same molecule the anæsthetic property appears. Other aliphatic radicals may be substituted for the methyl group without destroying the physiological activity of the substance; but substitution of other radicals for the benzoic acid residue lessens or destroys its activity. This fact has led to the investigation of many benzoic acid derivatives, and some of them have proved to be capable of producing

local anaesthesia. The most successful substitute for cocaine, namely, novocaine, belongs to this group:\*



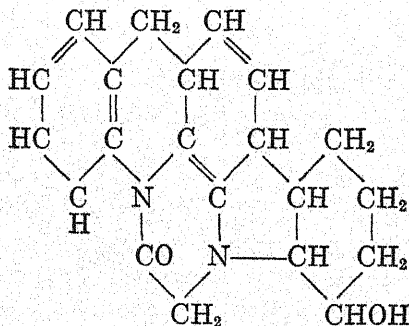
The free novocaine base is insoluble in water.

### STRYCHNINE

Strychnine,  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$ , occurs with brucine,  $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4$ , in the nuts or seeds, leaves, and bark of the plants of the genus *Strychnos*. *Nux vomica*, the seed of *Strychnos nux vomica*, contains more than one per cent of strychnine and as much brucine. Curare, a resin extracted from many species of trees, contains strychnine, brucine, curarine, and other poisonous bases.

Strychnine crystallizes in prisms (m.p.  $268^\circ$ ) which are soluble in alcohol and practically insoluble in water.† It is lævoptatory, and has an alkaline reaction and a bitter taste.

The structure of the strychnine molecule has not been determined. Quinoline and indol have been isolated from the decomposition products obtained by fusing the alkaloid with caustic potash, and pyridine has been obtained from it by distillation with lime. It possesses a carbonyl group, an alcoholic hydroxyl group, a reduced benzene ring, a quinoline residue, and an indol group; and from these considerations Perkin and Robinson have proposed the formula given below. This structure accounts for the reactions of strychnine, but until it is confirmed by actual synthesis it must be regarded as tentative only:



\* For a discussion of compounds related to novocaine see Meyer and Gottlieb's "Pharmacology."

† Strychnine salts are soluble in water. The sulfate is generally used.

Instead of obtaining normally coördinated movements, in response to definite stimuli, every stimulus affecting the sensory organs of a victim of strychnine poisoning causes simultaneous contractions of all the skeletal muscles. These tetanic convulsions may last for a few seconds or for several minutes. After several convulsions paralysis develops and death results from exhaustion of the nervous system. The lethal dose is about 0.1 of a gram.

### MORPHINE

The dried sap of some species of poppies constitutes a waxlike substance known as opium. It is a mixture of gums, resins, carbohydrates, fats, proteins, salts, and alkaloids. The chief representative of the group of vegetable bases in opium is morphine,  $C_{17}H_{19}NO_3$ .

Morphine is a colorless, crystalline base which melts and decomposes at  $247^{\circ}$ . It is only slightly soluble in water, benzene, chloroform, and ether, but it dissolves readily in alcohol. Its solutions are alkaline, bitter, and lævorotatory.

The constitution of morphine has not been fully established. It is a tertiary base with a methyl group attached to the nitrogen. It is a phenanthrene derivative, a phenol, and an ether.

Codeine is a methyl ether of morphine. The quantity of codeine in opium is usually less than 0.5 per cent, whereas morphine constitutes from 6 to 10 per cent of the substance. Twenty different alkaloids have been identified as components of opium, but with the exception of morphine, narcotine, papaverine, thebaine, and codeine they are present in mere traces.

Morphine produces a variety of effects in various species of animals. In human beings it acts as a sedative, small doses causing sleep and toxic doses producing profound unconsciousness. Its most important therapeutic use is that of relieving pain, which is accomplished in most cases by administration of less than 0.01 of a gram. The ability to perceive pain is depressed by doses much too small to cause sleep.

Although no other drug stands in the same class with morphine in respect to relieving pain, its use must be carefully curtailed, for, like other opium alkaloids, it develops in the patient a desire to have the treatment repeated even when he is free from pain. It is the most powerful habit-forming drug known.\*

\* For a vivid description of the physiological effects of morphine read De Quincey's "Confessions of an English Opium-Eater."

Acute morphine poisoning is caused by doses ranging from 0.03 to 0.06 of a gram. The average lethal dose for an adult unaccustomed to its use is about 0.35 of a gram. The system acquires tolerance for morphine, and habitual users take large doses with impunity. The effects described above are produced by much smaller quantities of the alkaloid if administered by hypodermic injection.

### CINCHONINE AND QUININE

According to a South American tradition dating back to 1638, the Countess of Chinchon recovered from a fever after drinking an extract from the bark of a tree. The generic name *Cinchona* was later applied to the trees yielding similar products, and the first alkaloid isolated from the bark was called cinchonine.

Cinchonine,  $C_{19}H_{22}N_2O$ , crystallizes in prisms melting at  $255^\circ$ . It is a strong ditertiary base, dextrorotatory, almost insoluble in water, soluble in alcohol, and much like quinine in its chemical and physiological reactions. Quinine is a methoxy derivative of cinchonine. The two alkaloids occur together, and they are usually associated with traces of at least twenty other related bases.

Quinine is the most important member of the group. It is a drug of great therapeutic value. It is not a poison in the ordinary sense of the term; still it is far from harmless if taken in large doses. It retards all vital processes, inhibiting every type of metabolic change. Quinine is used quite generally to combat fevers. Its efficacy, however, depends to some extent upon the nature and origin of the disorder. Its germicidal action on the malarial organism is specific, and it probably plays a similar rôle in the treatment of typhoid fever.

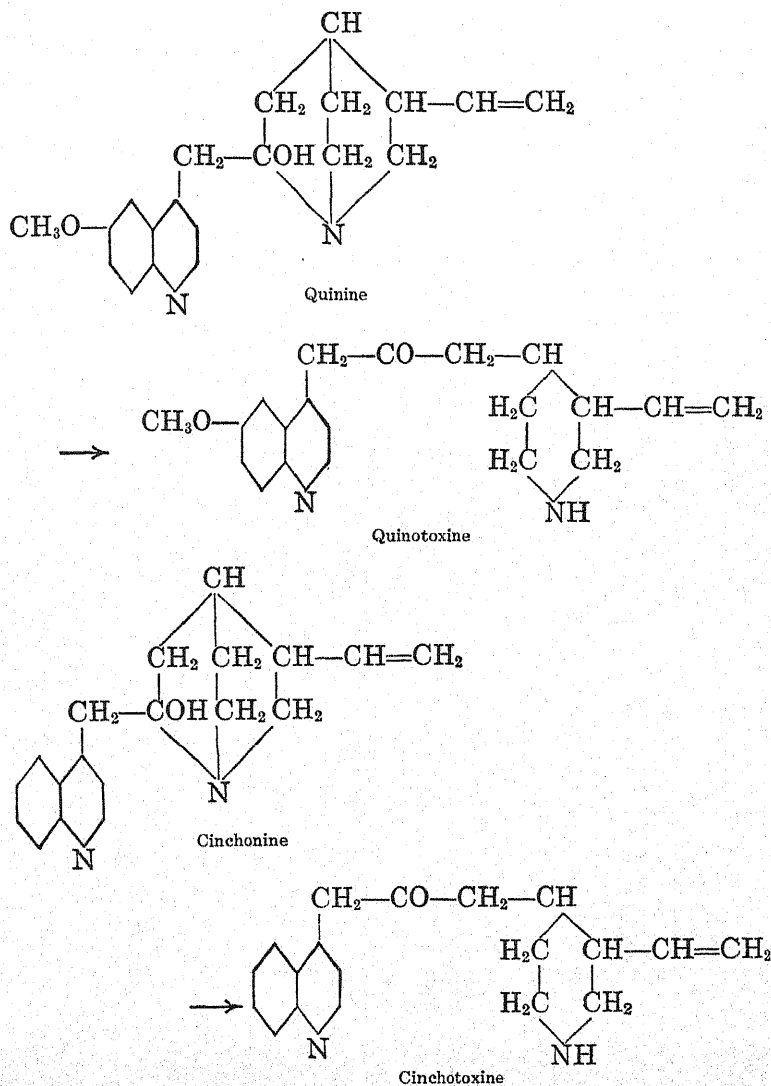
Quinine and cinchonine are converted into toxic isomers through the agency of acetic acid or citric acid. The change consists of the migration of a hydrogen atom from carbon to nitrogen, converting an enol into a keto structure.

Biddle\* discovered that the rate of change of quinine into quinotoxine, or cinchonine into cinchotoxine, is proportional to the concentration of undissociated acid present, the rearrangement being inhibited by hydrogen ions. Sallmann† denies

\* Biddle, *J. Am. Chem. Soc.*, **37**, 2088 (1915).

† Sallmann, *J. Am. Med. Assoc.*, **76**, 999 (1921).

that there is any danger in the use of quinine with an organic acid, for he maintains (1) that the conversion proceeds so slowly that only traces of quinotoxine could be formed during the few hours the drug remains in the stomach, (2) that the conversion cannot occur in the alkaline medium of intestinal fluids, and (3) that quinotoxine is not as poisonous as it is commonly believed to be.

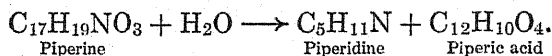




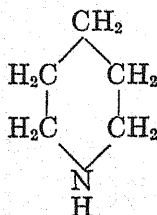
## PIPERINE

A crystalline alkaloid known as piperine,  $C_{17}H_{19}NO_3$ , is found in the berries of the pepper tree. It is almost insoluble in water, but dissolves in alcohol. It melts at  $128^\circ - 129^\circ$  and is optically inactive. It is a very weak base, neutral to litmus, and insoluble in dilute acids. It forms salts with concentrated hydrochloric, sulfuric, and nitric acids, but these addition products are rapidly and completely hydrolyzed when dissolved in water, the free base being precipitated.

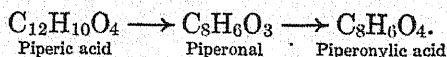
Piperine is hydrolyzed by an alcoholic solution of potassium hydroxide, the products being piperidine and piperic acid :



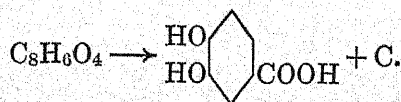
The constitution of piperidine is known. It is formed from cadaverine (pentamethylenediamine) by loss of ammonia, and is easily oxidized to pyridine. Its structural formula is



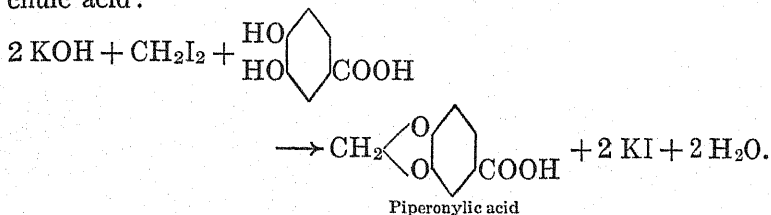
Piperic acid,  $C_{12}H_{10}O_4$  (m.p.  $217^\circ$ ), is an unsaturated mono-basic acid. It is only slightly soluble in water, but dissolves readily in carbon disulfide, and can be titrated with a standard solution of bromine in carbon disulfide. It absorbs four bromine atoms per mole of acid. The unsaturation, therefore, corresponds to the presence of two double bonds. Potassium permanganate oxidizes piperic acid to an aldehyde, piperonal, and finally to the corresponding acid, piperonylic acid :



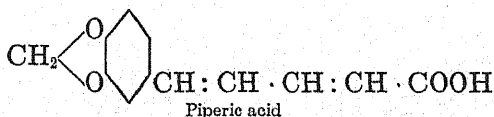
Piperonylic acid (m.p.  $228^\circ$ ) is decomposed by hydrogen iodide at  $180^\circ$ , or by water vapor at  $225^\circ$ , with the formation of 3, 4-dihydroxybenzoic acid and carbon :



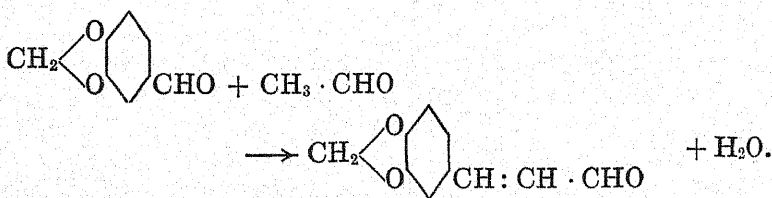
It is regenerated from 3,4-dihydroxybenzoic acid (protocatechuic acid) by treatment with methylene iodide and an alkali. Piperonylic acid is, therefore, the methylene ether of protocatechuic acid:



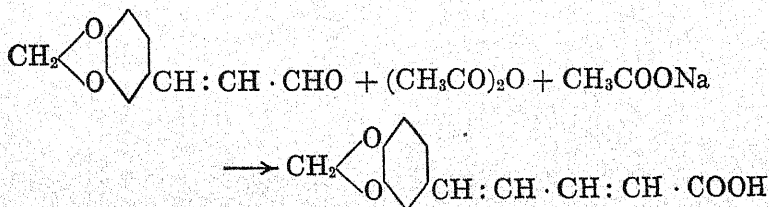
Piperic acid differs from piperonylic by  $\text{C}_4\text{H}_4$ , and since the latter has only one carboxyl group attached to the ring, and is derived from piperic acid by oxidation, the  $\text{C}_4\text{H}_4$  and the carboxyl group belong to the same side chain. Moreover, the side chain must be unsaturated to account for the absorption of four bromine atoms. The following structure meets these demands:



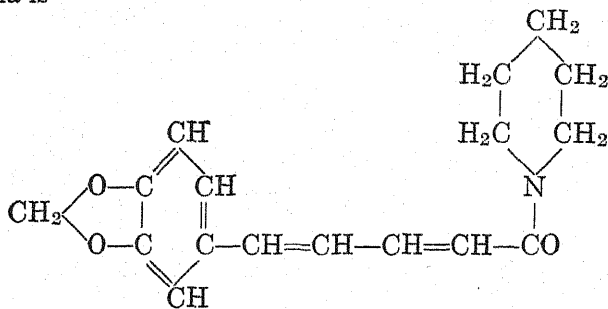
This structure has been confirmed by a synthesis of the acid. Piperonal and acetaldehyde, when dissolved in very dilute alkali and warmed, yield piperonylacrolein:



This aldehyde condenses with acetic anhydride and sodium acetate, yielding piperic acid:



Piperine is a condensation product of piperic acid and piperidine. On hydrolysis it yields these compounds. Hence its formula is



Piperine

## ESSENTIAL OILS

Volatile oils, characterized by agreeable odors or flavors, may be extracted from the leaves and bark of many trees and from flowers. Such extracts have been used as flavors and perfumes since the dawn of history. They are known as essences or essential oils.

Incense has been used in certain forms of religious worship for many centuries, fragrant roots, stems, or leaves being burned to release the volatile and aromatic constituents. In the earliest writings of the Chinese, the Greeks, and the Egyptians, reference is made to the use of herbs for the preparation of perfumes. Fragrant ointments (balms) were employed by the early Egyptians for the treatment of wounds and for preserving dead bodies (embalming).

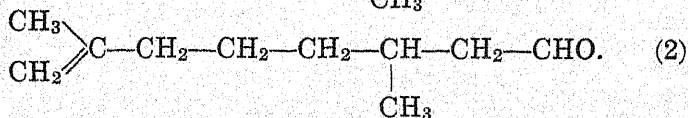
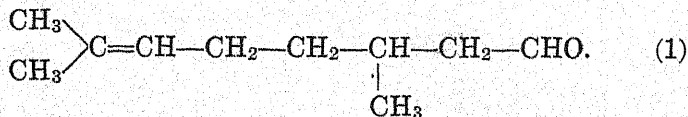
Many of the volatile extracts from plants consist chiefly of hydrocarbons having the formulas  $C_5H_8$ ,  $C_{10}H_{16}$ , and  $C_{15}H_{24}$ , called hemiterpenes, terpenes, and sesquiterpenes, respectively, or of compounds derived from these hydrocarbons by oxidation. Even in essential oils that are composed primarily of hydrocarbons the characteristic odors and flavors are due to the presence of oxygen compounds, including phenols, alcohols, esters, aldehydes, and ketones. In comparatively few cases do we find the origin of these properties in hydrocarbons. Many of the flavors and perfumes on the market today are synthetic products. In most instances the artificial preparation contains the identical chemical compound that imparts the desired scent or taste to the natural extract. In other cases these properties are merely imitated by substitution of other types of compounds having flavors or odors similar to those of the natural products. It must be remembered, however, that the extract from a leaf or a flower contains a large number of aromatic bodies, whereas the corresponding synthetic product contains, as a rule, only the one chemical substance that has been found to yield what we recognize as the characteristic odor or taste of the natural extract. On that account the two preparations are not identical.

## TERPENES

A dozen or more liquid hydrocarbons and at least two crystalline compounds corresponding to the formula  $C_{10}H_{16}$  constitute the group known as terpenes. Most of them occur in nature, but a few members of the group are synthetic products of the laboratory only. They fall into three general classes: (1) open-chain or olefinic terpenes, (2) monocyclic terpenes, and (3) bicyclic terpenes. The first group consists of unsaturated open-chain polymers of isoprene that are more or less readily converted into cyclic derivatives. Members of the second group contain one closed ring, and either in the ring, or in side chains, or distributed between the two, they have two double bonds. The bicyclic or bridged-ring terpenes have only one double bond. The second and third classes may be regarded as derivatives of methylisopropylbenzene (cymene) or of menthane, which is hexahydrocymene.

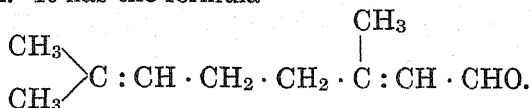
## OLEFINIC TERPENES AND THEIR DERIVATIVES

*Citronellal*. As a representative of the group we may consider first citronellal,  $C_{10}H_{18}O$ . It occurs in eucalyptus oil and in the oils of citrus fruits. It is a colorless liquid, boiling at  $208^{\circ}$ . Citronellal is an aldehyde, for it reacts with hydroxylamine and other reagents that attack the carbonyl group; and it yields an acid with ten carbon atoms if treated with a mild oxidizing agent. It is readily reduced to an alcohol. Vigorous oxidation converts it into acetone,  $\beta$ -methyladipic acid, and other products. Studies of the reactions of citronellal have led to the conclusion that it is not a pure chemical compound but a mixture of two aldehydes corresponding to the following structures:\*



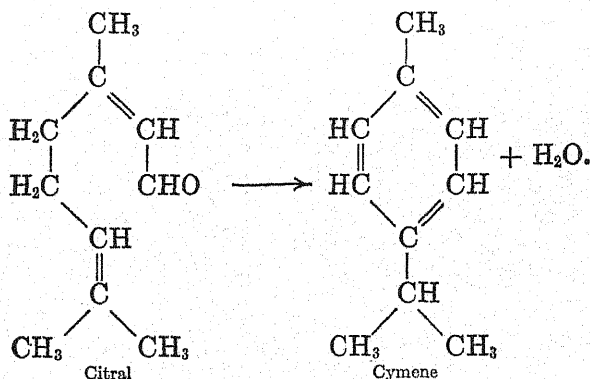
\* For a full discussion of the structure of citronellal see J. L. Simonsen's "The Terpenes." Cambridge University Press, 1931.

*Citral*. Closely related to citronellal is another aldehyde, citral or geranial,  $C_{10}H_{16}O$ , representing a higher state of unsaturation. It has the formula

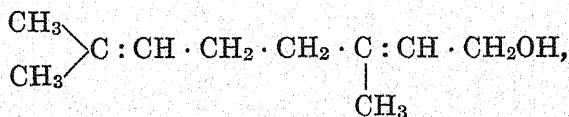
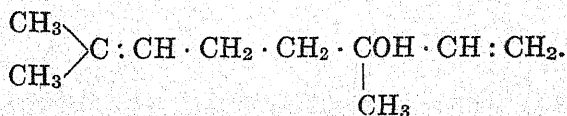


Citral

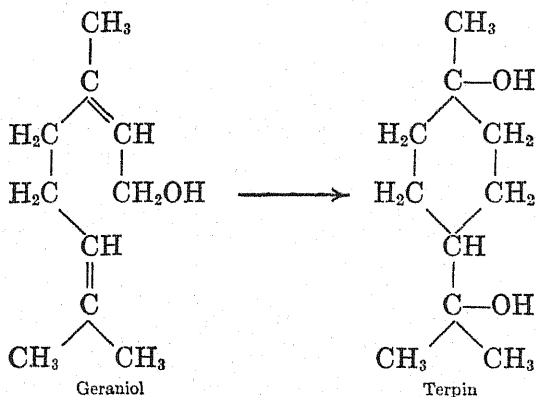
Citral occurs in the oil expressed from lemon and orange peel. It is a mobile, colorless liquid (b.p.  $228^\circ$ ), having a strong lemon odor. Lemon oil contains less than 10 per cent of citral, but lemon-grass oil is rich in this substance (60 to 80 per cent), and is the chief commercial source of the compound. It is dehydrated slowly by shaking it with dilute sulfuric acid and potassium bisulfate. The product formed is the cyclic hydrocarbon, cymene:



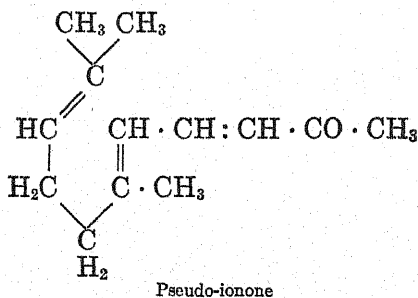
*Geraniol and linaloöl*. Geraniol, occurring in geranium oil, and linaloöl, found in oil of lavender, bergamot, and elsewhere, are related to citral, as indicated by the formulas,

Geraniol (b.p.  $229^\circ$ )Linaloöl (b.p.  $198^\circ$ )

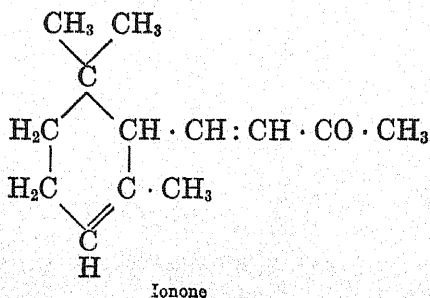
Geraniol may be converted into citral by oxidation with chromic acid or into linaloöl by the action of steam at 200°. Geraniol and linaloöl, when shaken with 5 per cent sulfuric acid, are converted into terpin by addition of water:



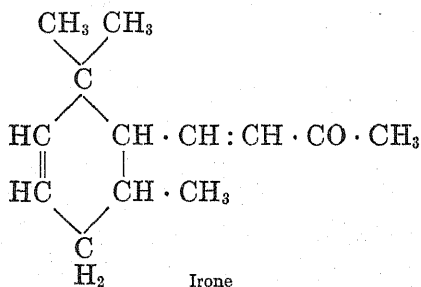
*Ionone and irone.* Geranial (citral) forms a condensation product with acetone, water being eliminated in the reaction. The substance formed is pseudo-ionone:



Warm, dilute sulfuric acid converts pseudo-ionone into ionone,



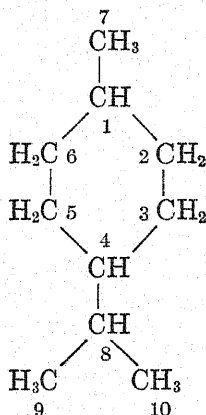
Ionone has the odor of violets and is manufactured for use in perfumes. It differs from irone, the natural violet product, only in the position of the double bond in the ring:



Both are colorless liquids, very slightly soluble in water but soluble in alcohol and in ether.

### MONOCYCLIC TERPENES

The monocyclic terpenes may be regarded as derivatives of the saturated hydrocarbon menthane, or hexahydrocymene. As a basis for a systematic nomenclature the carbon atoms of menthane are numbered as follows:



A derivative of this compound with one double bond is a menthene, with two double bonds a menthadiene, etc. The position of a double bond is indicated by the symbol  $\Delta$  with an index number referring to the first carbon atom involved in the double linkage. If, in order to avoid ambiguity, both of the

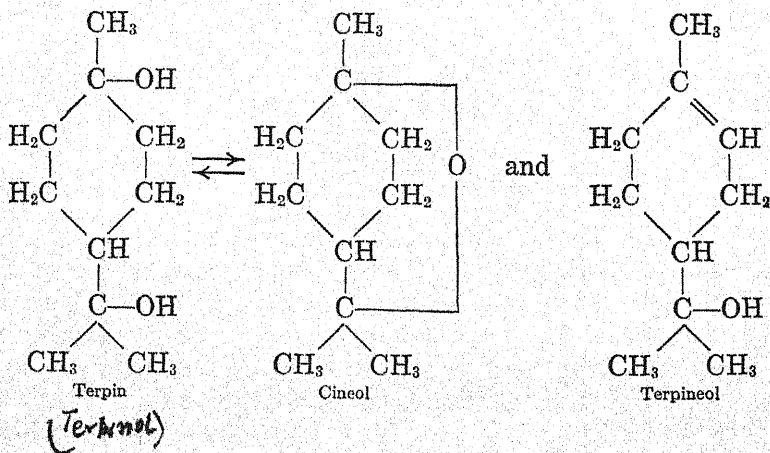


doubly linked carbon atoms must be specified, the number corresponding to the second carbon is written within parentheses. Thus the name  $\Delta^{2,4(8),5}$  menthatriene indicates that the compound is a menthane derivative with double bonds between carbon atoms 2 and 3, 4 and 8, 5 and 6. Carbon atom 8 must be specified, since number 4 may be doubly bound to either 5 or 8.

The most abundant of all essential oils is turpentine, obtained from the sap of pine trees. It is a mixture of several terpenes and resins. Ordinary rosin is a solid residue obtained by distilling turpentine. Turpentine boils between  $155^{\circ}$  and  $160^{\circ}$  and has a specific gravity of about 0.86. Since it is not a pure compound, these properties vary with the source of the oil. It is insoluble in water, but dissolves in alcohol, benzene, or ether. It is a good solvent for phosphorus, sulfur, iodine, rubber, and the resins used in the manufacture of paints and varnishes. The chief constituent of turpentine is pinene, a bicyclic compound to be described later. Dipentene, a mixture of *d*- and *l*-limonene, and some other monocyclic terpenes also are present. On exposure to air turpentine is slowly oxidized and resinified.

*Terpin*,  $C_{10}H_{20}O_2$ , an oxidation product of turpentine, is prepared by dissolving turpentine in alcohol and allowing the solution to stand in contact with cold dilute nitric acid for about a week. Water is taken up by the turpentine, and crystals of terpin hydrate (m.p.  $117^{\circ}$ ) are formed. Anhydrous terpin melts at  $104.7^{\circ}$  and boils at  $258^{\circ}$ . Its synthesis from geraniol has been mentioned.

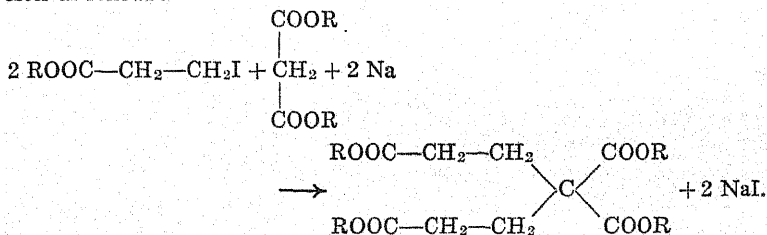
*Cineol* and *terpineol* are obtained from terpin by shaking the latter with hot dilute sulfuric acid :



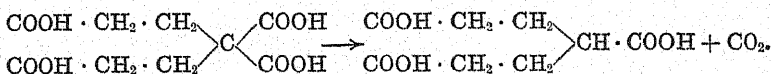
Cineol is a liquid (b.p. 177°) with a camphor-like odor; terpineol is a solid (m.p. 35°, b.p. 219.8°) which crystallizes readily when the mixture is cooled. The reaction indicated above is reversible. Terpin is dehydrated by hot dilute sulfuric acid and regenerated slowly from cineol and terpineol in the same solution at low temperatures.

The question as to which of the hydroxyl groups in terpin is removed in the formation of terpineol was settled when it was found that the terpineol formed is a racemic mixture of optically active forms. Carbon atom 4 is asymmetric in the formula given, but asymmetry could not be produced by removing the hydroxyl group from carbon atom number 8 with hydrogen from any adjacent carbon atom.

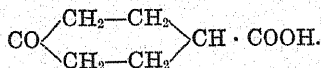
The constitution of terpineol has been established also by direct synthesis. For example,  $\beta$ -iodopropionic ester reacts with sodium and malonic ester as follows:



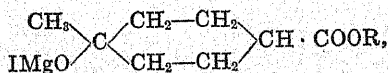
This ester is hydrolyzed by boiling with dilute hydrochloric acid, and when warmed, the free acid loses carbon dioxide:



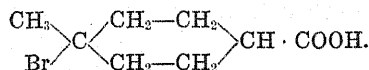
When distilled this product yields water and one more molecule of carbon dioxide and is converted into a closed-ring compound,—keto-hexahydrobenzoic acid:



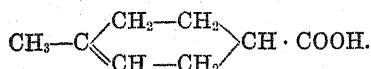
Methyl magnesium iodide reacts with an ester of this acid, the ketone group of the ring being first attacked. The addition product,



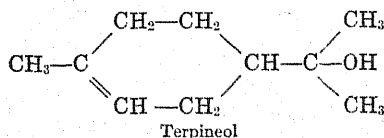
is hydrolyzed, and the resulting methyl-hydroxy-hexahydrobenzoic ester is subjected to the action of fuming hydrobromic acid. The hydroxyl group is thus replaced by bromine, the product being



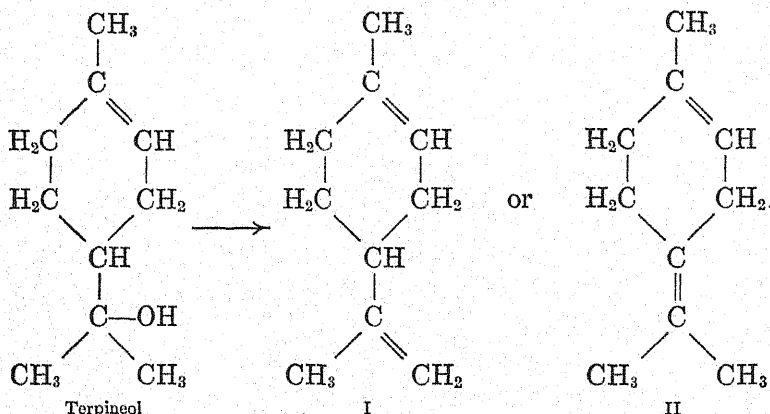
Dilute sodium or potassium hydroxide or even pyridine removes hydrogen bromide from this compound, establishing a double bond in the ring:



This is esterified once more, treated with an excess of the Grignard reagent ( $\text{CH}_3\text{MgI}$ ), and hydrolyzed. The resulting product is terpineol,



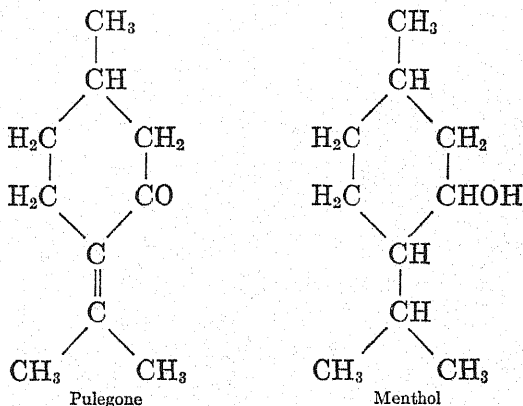
*Dipentene.* Terpineol yields one molecule of water and is converted into dipentene when heated with potassium hydrogen sulfate. There are two possible mechanisms for this dehydration:



Dipentene is a racemic mixture of optically active hydrocarbons known separately as *d*- and *l*-limonene, and therefore corresponds to formula I, in which carbon atom 4 is asymmetric. There is no asymmetric carbon atom in II. Formula II is assigned to another compound, terpinolene, an optically inactive

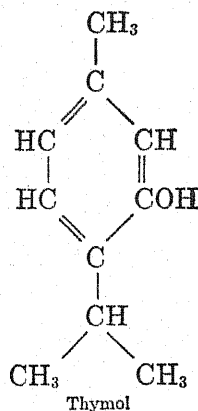
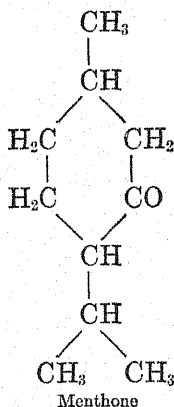
hydrocarbon incapable of resolution into active forms and obtained from terpineol when the latter is dehydrated by means of a mixture of alcohol and sulfuric acid. Dipentene is a constituent of pine-needle oil, citronella oil, and oil of cubebs. The optically active forms (limonenes) are widely distributed in nature, *d*-limonene being present in lemons, oranges, caraway, dill, and bergamot, and *l*-limonene occurring in spearmint and peppermint. The limonenes are characterized by the formation of crystalline addition products with nitrosyl chloride. The reaction is carried out by adding to the terpene a solution of amyl nitrite and hydrogen chloride in glacial acetic acid. A new asymmetric carbon atom appears as a result of the addition, so that four isomeric derivatives corresponding to the formula  $C_{10}H_{16}NOCl$  are formed.

*Pulegone and menthol*, found in oil of peppermint, are important oxidation products of menthane:



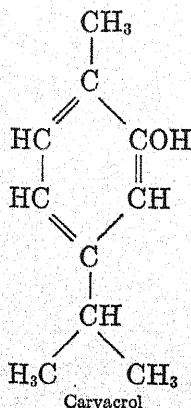
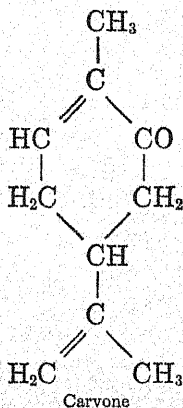
Sodium amalgam acts upon an alcoholic solution of pulegone, converting it into menthol. Menthol crystallizes from peppermint oil in slender, colorless needles. It is quite volatile, melts at  $43^\circ$ , and is used therapeutically for some disorders of the nose and throat. The structure assigned to menthol is based upon its conversion into menthane by reduction and into a ketone, menthone, by oxidation. The first process indicates its relationship to cymene, and the second shows that it is a secondary alcohol. The position of the hydroxyl group is determined by forming a dibromo derivative of menthone and subsequently eliminating two molecules of hydrobromic acid

by means of quinoline. Enolization of the compound is accomplished at the same time. The resulting unsaturated compound is thymol.



When thymol is heated with phosphoric acid, it yields propylene and *m*-cresol. The hydroxyl in thymol is thus proved to be *meta* to the methyl group, and hence the carbonyl group in menthone and the secondary alcohol group in menthol must be *meta* to the methyl radical. Menthone is an intermediate oxidation product between menthol and pulegone. The position of the carbonyl group in the latter is thus established.

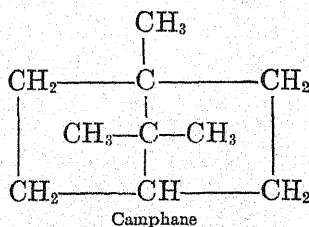
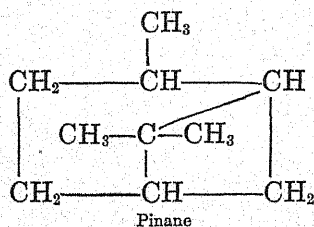
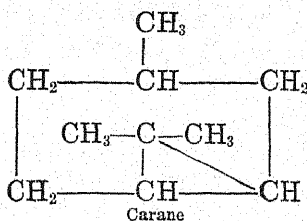
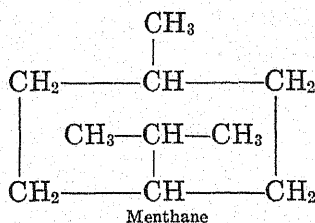
*Carvone and carvacrol.* The same process of reasoning is used in assigning a definite structure to carvone, a ketone found in oil of caraway, and to carvacrol, obtained from carvone by heating with an alkali:



The latter yields propylene and *o*-cresol when warmed with phosphoric acid. This result indicates that the carbonyl group in carvone and the hydroxyl group in carvacrol must be in the *ortho* position with respect to the methyl group.

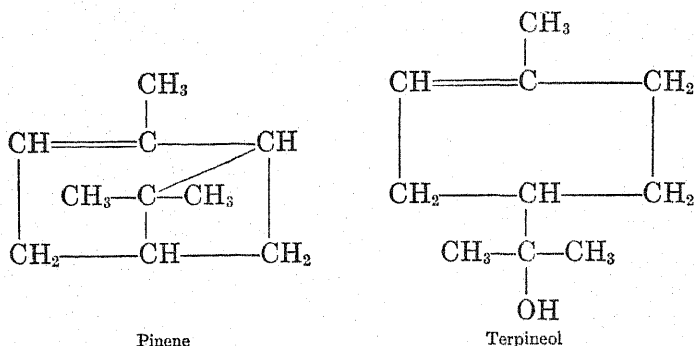
### DICYCLIC TERPENES

The principal dicyclic, or bridged-ring, terpenes are derivatives of pinene and camphene. Turpentine contains representatives of this series, isomeric with limonene, but capable of forming addition products with only two atoms of bromine or one molecule of hydrobromic acid. That is to say, each molecule in this group has only one double bond, although it has four hydrogen atoms less than the saturated hydrocarbon menthane. They are capable of conversion into terpin, terpineol, or limonene, and therefore, to account for their degree of unsaturation, they must have two closed chains, that is, two rings. There are three ways of forming a second ring or a "bridged ring" in the menthane molecule, with loss of two hydrogen atoms. Representatives of the three types of compounds are shown in the following structures:

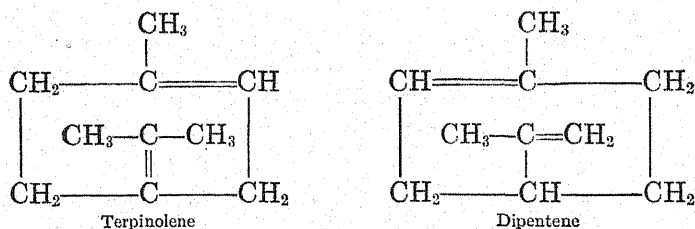


Pinene, the principal component of turpentine, differs from pinane by two hydrogen atoms. The position of the double bond is determined by the fact that pinene takes up a molecule

of water in the presence of acetic acid and benzenesulfonic acid, breaking the bridge and yielding terpineol:



The conversion of pinene into dipentene, which can be accomplished through the agency of an alcoholic solution of sulfuric acid, no doubt involves the formation of terpineol as an intermediate product. Removal of water from terpineol yields either terpinolene or dipentene, depending upon the conditions, and in either case the product is isomeric with pinene:

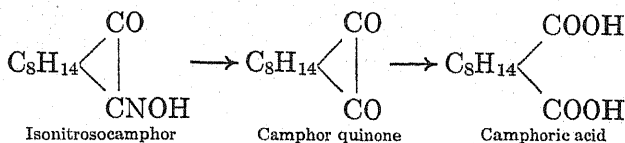


Pinene forms an addition product with hydrogen chloride, the double bond being broken. The compound resembles camphor and is sold as artificial camphor.

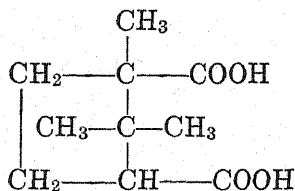
*Camphor.* The chief component of the essential oil obtained, by steam distillation, from the leaves of the camphor tree is a white, crystalline solid called camphor,  $\text{C}_{10}\text{H}_{16}\text{O}$ . It sublimes at low temperatures, melts at  $179^\circ$ , and boils at  $209.1^\circ$ . It is almost insoluble in water but dissolves in organic solvents.

Camphor is a ketone, for it reacts with hydroxylamine, forming an oxime. It contains the group  $-\text{CH}_2-\text{CO}-$ , for it yields an isonitroso derivative with nitrous acid. Hydrolysis of the

isonitroso compound results in the formation of camphor quinone, which is easily oxidized to camphoric acid :

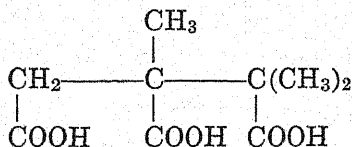


Camphoric acid is oxidized by a dilute solution of permanganate ion, the principal products being oxalic acid and  $\alpha\beta\beta$ -trimethyl- $\gamma$ -oxyglutaric acid. On the basis of this reaction the following structure has been assigned to camphoric acid :

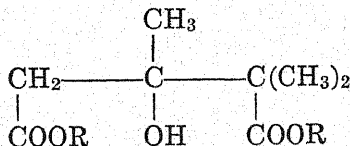


The structure has been confirmed by a synthetic preparation of the acid.\*

Nitric acid converts camphor into camphoronic acid,  $\text{C}_9\text{H}_{14}\text{O}_6$ . The structure of camphoronic acid is known to be



for it has been synthesized as follows: condensation of isobutyric ester and acetoacetic ester yields



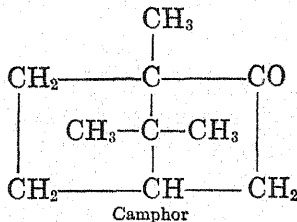
The hydroxyl group is replaced by chlorine through the agency of  $\text{PCl}_3$ . The chlorine is then replaced by CN through the

\* G. Komppa, *Ber.*, 36, 4332 (1903). G. Komppa and O. Routala, *Ber.*, 44, 858 (1911).

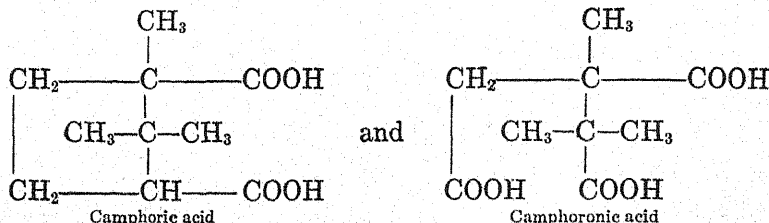


action of KCN, and the cyanide is then converted into the corresponding acid by hydrolysis.

On the basis of this evidence and in harmony with all its properties, Brett has assigned to camphor the following formula :



The primary oxidation products are



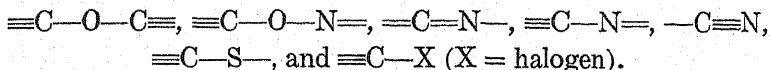
Camphor may be made from turpentine for about the same price that is now paid for the natural product. The most successful method consists of six steps, as follows: (1) Preparation of fairly pure pinene (b.p. 154°) from crude turpentine by fractional distillation. (2) Conversion of pinene into pinene hydrochloride by saturating it with dry hydrogen chloride gas at 10° to 15°. The crystalline addition product is obtained by cooling the mixture to -15°, filtering, and recrystallizing from alcohol. It is a soft, snow-white mass of very fine crystals (m.p. 128°) having an odor like that of camphor. (3) Preparation of camphene from pinene hydrochloride by digestion with potassium phenolate and subsequent fractional distillation. Camphene distills at 150° to 160°, and therefore is readily separated from the major portion of the phenol (b.p. 182°). Some phenol distills over with the camphene and is washed out by shaking with a solution of sodium hydroxide. The camphene is melted, dried with calcium chloride, and redistilled (m.p. 52°, b.p. 150°). (4) Preparation of isobornylacetate from camphene. This is done by warming camphene with glacial acetic acid and a little sulfuric acid. The product is washed, neutralized with sodium carbonate, and finally distilled in vacuo. It is a liquid, boiling at 102° at 12 mm. (5) Hydrolysis of isobornylacetate. The ester is heated on a steam bath with an alcoholic solution of potassium hydroxide. Isorneol separates as a colorless or slightly yellow crystalline solid (m.p. 212°). (6) Conversion of isorneol to camphor. This is done by oxidizing isorneol with fuming nitric acid at 20°-25°. The reaction mixture is poured upon cracked ice, and camphor separates as a soft, white, crystalline mass. It is purified by steam distillation (m.p. 179°).

# GENERAL ORGANIC REACTIONS

## HYDROLYSIS

An ordinary double decomposition in which water is one of the reagents is called hydrolysis. Some compounds are hydrolyzed by water alone and at low temperatures; others require the aid of a catalyst, or a high temperature, or both.

The structures most susceptible to hydrolysis are



An ether such as  $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{O} \cdot \text{CH}_2 \cdot \text{CH}_3$  is not readily hydrolyzed. In the presence of hydrogen ions at high temperatures it reacts with water, slowly forming alcohols. If, however, negative elements or groups be substituted for hydrogen on carbon atoms near the point where cleavage of the molecule occurs, the hydrolysis proceeds readily. The ester  $\text{CH}_3 \cdot \text{CO} \cdot \text{O} \cdot \text{CH}_2 \cdot \text{CH}_3$  may be partially hydrolyzed by water at ordinary temperatures without a catalyst. An accumulation of negative groups enhances the tendency to hydrolyze. Thus acetic anhydride,  $\text{CH}_3 \cdot \text{CO} \cdot \text{O} \cdot \text{CO} \cdot \text{CH}_3$ , takes up water more rapidly than does ethyl acetate.

The same principle applies to aromatic compounds. Chlorobenzene is not affected by boiling water. Trinitrochlorobenzene is hydrolyzed to picric acid with great ease. In general, the factors influencing the rate of hydrolysis are (1) the structure of the molecule to be hydrolyzed, (2) the catalyst, (3) the temperature, (4) the solvent, and (5) the concentration of the solution with respect to the substance hydrolyzed. Some of these factors will be considered in connection with typical hydrolytic processes.

**Hydrolysis of sugar.** Cane sugar presents the first structure listed above, namely,  $\equiv\text{C}-\text{O}-\text{C}\equiv$ . It is hydrolyzed to dextrose and laevulose under the catalytic influence of hydrogen ions or by the enzyme invertase. The rate of conversion may

be followed with the aid of a polariscope, the cleavage being accomplished by a change in optical rotation.

If  $a$  represents the concentration of sugar in the original solution;  $b$ , its initial rotation;  $c$ , its rotation at the end of any interval of time  $t$ ; and if  $d$  is its final rotation (after the hydrolysis is complete), then the quantity  $x$  hydrolyzed may be calculated from measurements made at any time:

$$x = \left( \frac{b - c}{b - d} \right) a.$$

The hydrolysis of sugar follows the unimolecular law. The concentration of the water may be regarded as constant. This follows from the fact that the quantity of water used is always large as compared with the amount demanded by the equation representing the hydrolysis. The rate equation is

$$\frac{dx}{dt} = k(a - x) \quad \text{and} \quad k = \frac{1}{t} \log \frac{a}{a - x}.$$

A solution of cane sugar having an optical rotation of 46.75 was hydrolyzed by dilute hydrochloric acid at the rate indicated below.

| $t$ (minutes) | $d$ (rotation) | $k = \frac{1}{t} \log \frac{a}{a - x}$ |
|---------------|----------------|--|
| 0             | 46.75          |  |
| 15            | 43.75          | .00136                                 |
| 30            | 41.00          | .00133                                 |
| 60            | 35.75          | .00133                                 |
| 90            | 30.75          | .00135                                 |
| 120           | 26.00          | .00137                                 |
| 150           | 22.00          | .00132                                 |
| 210           | 15.00          | .00137                                 |
| 330           | 2.75           | .00146                                 |
| 510           | -7.00          | .00146                                 |
| 630           | -10.00         | .00135                                 |
| Infinite      | -18.70         |  |

To find the per cent of the sugar that was hydrolyzed at the end of fifteen minutes we have

$$\frac{46.75 - 43.75}{46.75 - (-18.70)} = \frac{3}{65.45} = 4.58 \text{ per cent.}$$

The rate of hydrolysis of cane sugar varies with the hydrogen ion concentration of the solution. A half-normal solution of

nitric acid accomplishes the change six times as fast as does tenth-normal nitric acid.

A salt of a weak acid usually retards the rate of hydrolysis — a fact that can be accounted for on the basis of its tendency to reduce the hydrogen ion concentration — but it is not obvious that salts like sodium chloride and potassium bromide, when used in connection with hydrochloric or hydrobromic acid, should accelerate the change. However, this effect has been observed.

A rise of temperature causes a marked increase in the rate of the reaction. In the presence of 0.25 *N* HBr cane sugar is hydrolyzed fifty times as fast at 55° as at 25°. Any change in the composition of the solvent affects the rate of chemical action. The addition of alcohol to an acidified aqueous solution of sugar results in a lowering of the rate of hydrolysis. The magnitude of the change in rate is many times greater than would be predicted on the basis of diminished ionization of the acid. Other reactions show similar effects. Ammonium cyanate is converted into urea thirty times as fast in alcohol as in water. The relative rates of formation of tetraethylammonium iodide from ethyl iodide and triethylamine in various solvents are approximately as follows: hexane, 1; ether, 4; xylene, 10; ethyl acetate, 100; allyl alcohol, 200; acetone, 300; benzyl alcohol, 700. The fact that the reaction proceeds seven hundred times as fast in benzyl alcohol as in hexane cannot be attributed to more frequent collisions of the reacting molecules. It must be due to some specific effect of the solvent that results in an activation of the reagents.

Enzymes usually act selectively. Yeast, for example, contains or produces an enzyme which hydrolyzes cane sugar but fails to act upon milk sugar. The specificity of enzyme action is even more strikingly exhibited in connection with the hydrolysis of polypeptides. Racemic polypeptides are hydrolyzed asymmetrically by enzymes. One isomer usually remains unattacked.

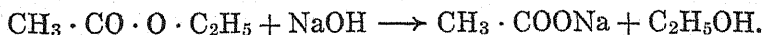
**Hydrolysis of an ester.** The reaction between water and ethyl acetate may be taken as a typical example of the hydrolysis of an ester:



The reaction is catalyzed by either hydrogen or hydroxide ions. Ordinarily water is used in large excess. Its concentration,

therefore, remains unchanged, and the velocity constant of the reaction corresponds to that of a unimolecular reaction.

When the reaction is carried out in alkaline solution, the base as well as the ester disappears:



In this case the reaction follows the bimolecular law. The velocity of the reaction is proportional to the product of the concentrations of the ester and of the base. If  $a$  and  $b$  represent the initial molal concentrations of ester and base, respectively, and  $x$  is the number of moles of esters and of base consumed in the time  $t$ , the rate is indicated by the equation

$$\frac{dx}{dt} = k(a - x)(b - x).$$

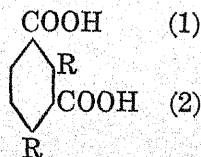
In an integrated form,

$$k = \frac{1}{t} \cdot \frac{1}{a - b} \cdot \left[ \log \frac{b(a - x)}{a(b - x)} \right].$$

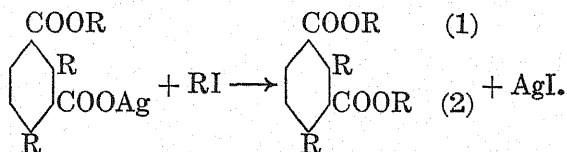
The rate of change may be followed by titrating measured samples of the mixture from time to time. The hydroxide ion concentration diminishes as the reaction proceeds. The value of  $k$ , in the equation given above, is constant when strong bases are employed. It is not constant when ammonium hydroxide is used. The ammonium salt formed is highly ionized and the accumulation of ammonium ions reduces the hydroxide ion concentration.

An ester of high molecular weight is hydrolyzed more slowly than one of lower weight, whether the difference in mass is due to the alcohol or to the acid in the ester. The methyl esters of acetic, propionic, butyric, and valeric acids are saponified under identical conditions at rates corresponding approximately to the numbers 50, 35, 12, and 10. Methyl, ethyl, propyl, and butyl acetates show nearly the same variations in rates.

Structural and stereochemical effects on saponification rates have been discussed, but a single illustration may be given here. In the dibasic acid



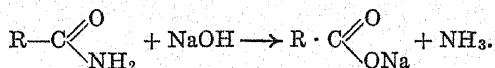
carboxyl group (1) is much more easily esterified than is carboxyl (2). Only one *ortho* substituent interferes with reactions of the former, whereas the latter, being protected by two *ortho* side chains, is esterified so slowly by the usual procedure (namely, treatment with an alcohol and hydrogen chloride gas) that this method is not used in actual practice. The second carboxyl group may be esterified, however, by the action of an alkyl iodide on the silver salt of the monoester:



Now, group (1) is much more readily hydrolyzed than is group (2). Hence by this indirect method either one or both of the carboxyl groups may be esterified.

**Other hydrolyses.** A cyanide or nitrile takes up one molecule of water, forming an amide, or two molecules of water, forming an acid. The first reaction is reversible, an amide,  $\text{RCONH}_2$ , being converted into the cyanide,  $\text{RCN}$ , and water by distillation with phosphorus pentoxide. A hot concentrated solution of hydrochloric acid is often used to convert the cyanide radical into a carboxyl group.

Amides are readily saponified by boiling with alkalis:



Sugars and starches are hydrolyzed, in the presence of acids, to monoses, and proteins are converted into peptones, amino acids, and other products, by acids or alkalis, or by enzymes.

Boiling with hydrochloric acid converts many oximes and hydrazones into the aldehydes or ketones from which they were derived.

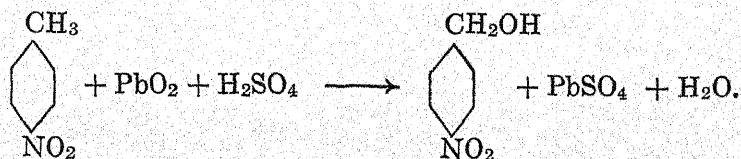
## OXIDATION

The oxidation processes most frequently used are designed to accomplish the following transformations: (1) an aliphatic side chain to carboxyl; (2) primary alcohol to aldehyde or acid; (3) secondary alcohol to ketone; (4) phenol to quinone; (5) methylene group to  $\text{—CHOH—}$  or to  $\text{—CO—}$ ; (6) oxime to peroxide; (7) hydroxylamine derivative to azoxy compound; (8) hydrazine derivative to azo body.

The principal oxidizing reagents used in organic chemistry are chromic acid, alkaline and acid solutions of permanganates, nitric acid, hydrogen peroxide, lead dioxide, silver oxide, mercuric oxide, nitrobenzene, bromine, hypobromites, ferric salts, amyl nitrite, and atmospheric oxygen. Many other reagents are used in special cases.

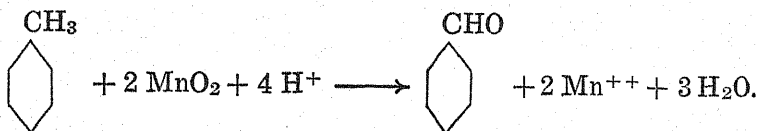
**Side chains.** An aliphatic side chain on a cyclic nucleus may be oxidized to carboxyl by such reagents as nitric and chromic acids. As a rule the chain is oxidized in such a way as to leave the newly formed carboxyl group attached to the ring. For an exception to this rule see page 198. Thus toluene, ethylbenzene, and propylbenzene all yield benzoic acid on oxidation. This means that the carbon atom attached directly to the ring represents the place that is most susceptible to oxidation. It is a reasonable assumption that oxidation begins there, forming a carboxyl group at once and eliminating the remainder of the chain, which subsequently yields carbon dioxide and water or acids of low molecular weight.

It is sometimes possible to obtain an aromatic alcohol or an aldehyde from a hydrocarbon by the oxidation of a side chain. Among the reactions of this kind we have the preparation of *p*-nitrobenzyl alcohol from *p*-nitrotoluene:





The commercial production of benzaldehyde from toluene is another example (see page 244) :



The temperature and time required for the maximum yield of an oxidation product are factors to be determined experimentally in every new reaction. For details concerning known reactions, we turn to the journals and handbooks. One finds, for example, that *o*-xylene and *p*-xylene are converted into the corresponding toluic acids by dilute nitric acid (1 vol.  $\text{HNO}_3$ , sp. gr. 1.4, to 3 vols.  $\text{H}_2\text{O}$ ), whereas *m*-xylene requires a concentration of nitric acid twice as great to yield *m*-toluic acid. Chromic acid converts *m*-xylene and *p*-xylene into the corresponding phthalic acids, both methyl groups being converted into carboxyl groups, but *o*-xylene is decomposed by similar treatment. The latter, however, is readily oxidized to *o*-phthalic acid by a hot alkaline solution of potassium permanganate.

The same general rules apply to side chains on heterocyclic rings. The methylpyridines are converted into picolinic, nicotinic, and isonicotinic acids by hot solutions of potassium permanganate. Alkyl derivatives of quinoline are usually oxidized by heating them on a water bath with dilute sulfuric acid and potassium dichromate. Methyl quinoline is thus converted into quinoline carboxylic acid.

**Alcohols.** Oxidation of a primary aliphatic alcohol results in the formation of an acid, unless the intermediate aldehyde escapes on account of its volatility or is removed by a reaction that is more rapid than the oxidation process. Some aromatic alcohols are more readily oxidized than the corresponding aldehydes, and the aldehydes in such cases may be obtained as final products. Dilute nitric acid converts benzyl alcohol into benzaldehyde. On the other hand, benzaldehyde is oxidized to benzoic acid by atmospheric oxygen and benzyl alcohol remains unchanged in the air. Aniline condenses rapidly with some aldehydes and may be used in such cases to prevent oxidation beyond the aldehyde stage. Esters are found among the oxidation products of alcohols, owing to the formation of acid molecules and their immediate combination with unchanged alcohol.



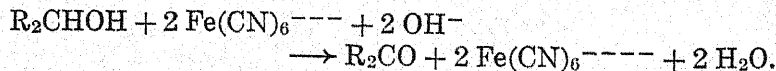
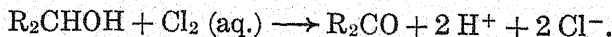
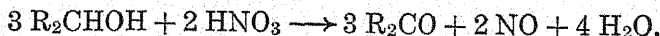
Ethyl alcohol yields acetaldehyde by the following procedure :

A mixture containing 25 g. of sodium dichromate, 25 g. of alcohol, and 40 g. of water is added in small portions to an equal volume of 50 per cent sulfuric acid. The mixture is boiled fifteen or twenty minutes under a reflux condenser, then distilled. A long, well-cooled condenser is used, and the receiver is packed in ice. Acetaldehyde boils at 20.8°. An aqueous solution of the aldehyde is obtained. It is purified by extraction with ether and conversion into the crystalline aldehyde ammonia, from which the pure aldehyde is obtained by distillation with dilute sulfuric acid.

Methyl alcohol is oxidized to formaldehyde by atmospheric oxygen when mixed with air and passed over hot platinum, copper, or nickel. Ethyl alcohol and other members of the same series having fewer than ten carbon atoms are oxidized to aldehydes and acids, without loss of carbon, by air in contact with finely divided metals at temperatures ranging from 150° to 650°. Alcohols of higher molecular weight yield carbon dioxide, acids of low molecular weight, and water.

Aromatic alcohols are oxidized by the same methods. In some cases aromatic halogen compounds (halogen in side chain) may be oxidized to aldehydes by lead nitrate solution. Benzyl chloride,  $C_6H_5CH_2Cl$ , when boiled with a solution of copper nitrate or lead nitrate, yields benzaldehyde. The process involves replacement of the halogen by hydroxyl and subsequent oxidation of the primary alcohol. Aromatic alcohols, dissolved in chloroform, are oxidized to aldehydes by nitrogen tetroxide. The reaction is slow, requiring several days, but it is almost quantitative.\*

Chlorine water, chromic acid, ferricyanides, and nitric acid are reagents commonly employed to convert secondary alcohols into ketones :

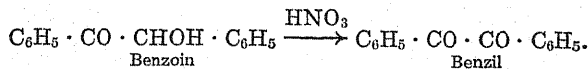


Polyhydric secondary alcohols containing no primary alcohol groups are oxidized to ketone alcohols by solutions of hydrogen peroxide and ferrous sulfate; hydroxy acids may usually be changed to ketone acids by permanganate ions, and diketones

\* Cohen and Calvert, *J. Chem. Soc.*, 71, 1050 (1897).

are derived from ketone alcohols through the action of nitric acid or an alkaline solution of copper salts. The details of one method may be given :

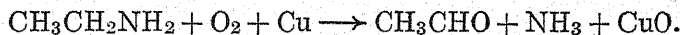
Dry powdered benzoin is heated on a water bath with twice its weight of pure concentrated nitric acid for two hours. The mixture is then poured into cold water. Benzil separates as a crystalline solid mass. It is washed with water until free from acid, then recrystallized from hot alcohol :



Tertiary alcohols are not easily oxidized. They can usually be recovered unchanged after treatment with an acetic acid solution of potassium dichromate under temperature conditions that insure the oxidation of primary and secondary alcohols. When a tertiary alcohol does respond to oxidation, it is converted into compounds of fewer carbon atoms.

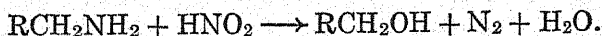
The conversion of an enol into a ketone, with loss of hydrogen and a concomitant change in the structure of the molecule, is, in some cases, accomplished with great ease (see indigo white, p. 287).

**Amines.** A warm solution of an alkyl amine in which fine copper powder is suspended absorbs oxygen and acquires a deep blue color. The blue solution, when acidified and distilled, yields an aldehyde :



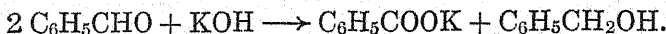
Aniline sulfate in dilute sulfuric acid is oxidized by dichromate ions at 0° to 10°. The reaction requires about twenty-four hours for completion. From the mixture quinone may be extracted with ether (yellow crystals, m.p. 115.7°). Intermediate products are formed, one of the first being phenylhydroxylamine. *Para*-aminophenol is derived from the latter by intramolecular rearrangement, and finally quinone is formed through oxidation of the aminophenol.

Primary aliphatic amines are converted into alcohols by nitrous acid. Phenols are derived from primary aromatic amines in the same way.



**Aldehydes.** The aldehyde group is especially susceptible to oxidation, Fehling's solution or silver oxide in ammonium

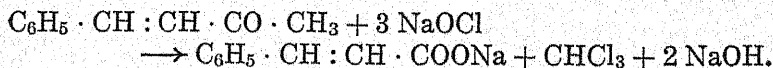
hydroxide being more serviceable than the stronger oxidizing reagents. Fehling's solution (alkaline copper tartrate) fails, however, to oxidize aromatic aldehydes. A method applicable to some of the aromatic aldehydes is treatment with a saturated solution of potassium hydroxide. Half of the aldehyde molecules are oxidized and half reduced:



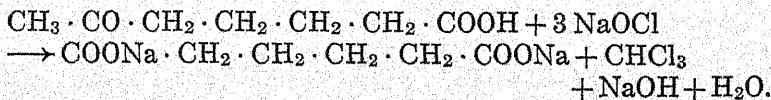
The activity of an oxidizing agent cannot be determined by studying a single reaction. Silver oxide, for example, rapidly oxidizes the aldehyde group,  $-\text{CHO}$ , but fails, in most cases, to break the ethylene linkage,  $-\text{C}=\text{C}-$ . On the other hand, potassium permanganate acts faster on the ethylene than on the aldehyde group.

**Ketones.** Chromic acid breaks the ketone molecule with the production of acids. From two to four acids are formed, the number depending upon the structure of the ketone. The cleavage may occur on either side of the carbonyl group. Ethylisobutyl ketone,  $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}(\text{CH}_3)_2$ , may form acetic and isovaleric acids, or it may split on the opposite side of the carbonyl group and form propionic and isobutyric acids. Usually the cleavage which leaves the ketone carbonyl attached to the shorter chain predominates. However, the principal oxidation products derived from acetonylacetic acid,  $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COOH}$ , are succinic acid and carbon dioxide. Ethylisopropyl ketone,  $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{CH}(\text{CH}_3)_2$ , is oxidized to propionic acid and acetone; small quantities of acetic and isobutyric acids are formed also. The acetone formed in the primary reaction is further oxidized and appears ultimately in the form of acetic and carbonic acids.

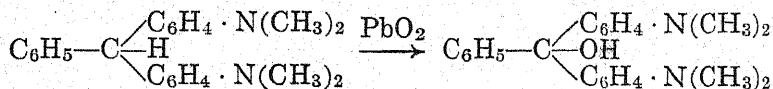
Saturated as well as unsaturated methyl ketones are oxidized by sodium hypochlorite, the methyl group being removed as chloroform. Thus benzalacetone yields cinnamic acid:



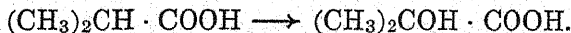
In the same way  $\epsilon$ -ketoheptylic acid forms adipic acid:



**Hydrocarbons.** A saturated aliphatic hydrocarbon, as a rule, cannot be converted into an alcohol by direct oxidation, for any reagent that oxidizes a hydrocarbon acts even more readily on an alcohol. The usual result of such a reaction is the production of water and carbon dioxide. However, hydrogen held by a tertiary carbon atom is quite easily oxidized to hydroxyl. From triphenylmethane a 90 per cent yield of triphenyl carbinol is obtained by treatment with chromic and acetic acids at the temperature of a water bath. Lead dioxide and sulfuric or hydrochloric acid serve to convert the leuco-base of malachite green into the color-base:



In many other types of compounds tertiary carbon displays the same susceptibility to oxidation. Thus an alkaline solution of potassium permanganate acts upon isobutyric acid, producing hydroxyisobutyric acid:



In a few cases hydroxyl groups are introduced into aromatic compounds by fusion with sodium or potassium hydroxide. The hydroxyl group does not always take the position of the replaced group, and the number of hydroxyl groups introduced when an aromatic compound is fused with sodium hydroxide does not always correspond to the number of negative substituents originally in the ring.

Most aromatic hydrocarbons resist the action of the ordinary oxidizing agents. A reagent that acts energetically enough to attack the ring converts it into carbon dioxide and water or other products of low molecular weight. A few of them, however, including anthracene, phenanthrene, and naphthalene, are quite easily converted into the corresponding quinones. Naphthalene is oxidized to phthalic acid by heating it with sulfuric acid in the presence of mercury. Anthracene forms a quinone instead of a nitro compound when warmed with nitric acid. On a commercial scale, anthraquinone is made by an electrolytic oxidation of anthracene.\*

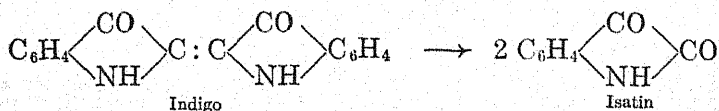
\* A lead anode is used in an aqueous solution of sulfuric acid (20 per cent) and vanadic acid (2 per cent); optimum current density, 800 amperes per square meter; temperature, 80°.

Benzene has been oxidized to quinone by silver nitrate, potassium persulfate, and nitric acid. Silver nitrate reacts with potassium persulfate in nitric acid, forming silver persulfate,  $\text{Ag}_2\text{S}_2\text{O}_8$ , which, with water, yields silver peroxide,  $\text{Ag}_2\text{O}_2$ , and sulfuric acid. As rapidly as the peroxide is used in the process the remaining silver or silver oxide is reconverted by the acid into the nitrate and by the potassium salt into persulfate. The silver is used repeatedly, and a small quantity suffices to decompose a large amount of the potassium persulfate.

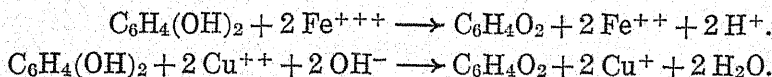
An unsaturated hydrocarbon is converted into a hydroxy derivative by shaking it with a 1 per cent solution of potassium permanganate. Ethylene yields ethylene glycol,



Cleavage in the position of a double bond with the formation of a ketone group is rather unusual, but an example is afforded in the action of nitric acid on indigo :



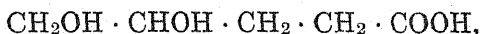
**Phenols.** *Ortho*- and *para*-dihydric phenols are readily oxidized to quinones. Thus hydroquinone is converted into quinone by a solution of a ferric salt or by an alkaline solution of copper sulfate :



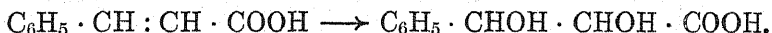
Quinones and other types of oxides are formed by the catalytic decomposition of the silver salts of some halogenated phenols. Ethyl iodide and iodine serve as catalysts in these reactions, bringing about the removal of silver and an *ortho*- or *para*-halogen in the form of silver halide.

**Unsaturated acids.** The addition of hydroxyl groups to unsaturated compounds is accomplished by the action of a very dilute alkaline solution of potassium permanganate at low temperatures. If there is only one double bond in the molecule, the hydroxyl groups are taken up by the two carbon atoms so bound ; but if there are two or more positions of unsaturation

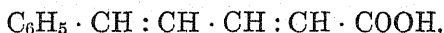
in the molecule, and especially in conjugate systems, hydroxyl groups may enter in 1-4 positions, or the molecule may cleave in the position of one double bond and add hydroxyl groups to the other. Thus when crotonic acid,  $\text{CH}_3 \cdot \text{CH} : \text{CH} \cdot \text{COOH}$ , is dissolved in dilute sodium hydroxide or sodium carbonate solution, cooled to  $0^\circ$ , and mixed with an equivalent quantity of 2 per cent potassium permanganate solution, a salt of dihydroxybutyric acid is formed. In the same way allyl-acetic acid,  $\text{CH}_2 : \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COOH}$ , is converted into  $\gamma$ - $\delta$ -hydroxyvaleric acid,



and cinnamic acid yields phenylglyceric acid:



On the other hand, cinnamenylacrylic acid,

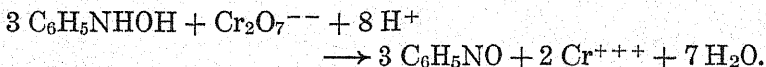
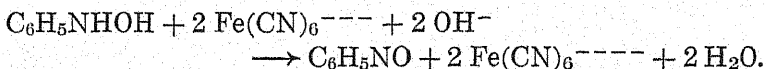


yields benzaldehyde,  $\text{C}_6\text{H}_5\text{CHO}$ , and tartaric acid,



Piperic acid, in the same way, yields piperonal and tartaric acid.

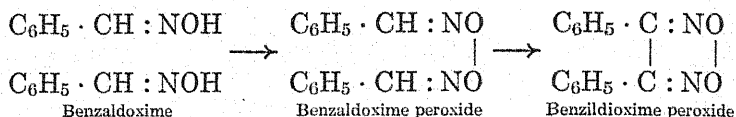
**Hydroxylamine derivatives.** Ferric chloride, mercuric oxide, and potassium ferricyanide are suitable reagents for the oxidation of aryl hydroxylamines. Very dilute solutions of permanganates or dichromates serve as well.



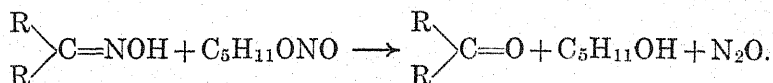
The following method is satisfactory for making nitrosobenzene:

Dissolve 2 g. of phenylhydroxylamine in 100 cc. of 6 per cent  $\text{H}_2\text{SO}_4$ , previously cooled to  $0^\circ$ . Add slowly, with stirring, 150 cc. of an ice-cold 2 per cent solution of sodium dichromate. Allow the mixture to stand at  $0^\circ$  for an hour, then extract the nitroso compound with ether.

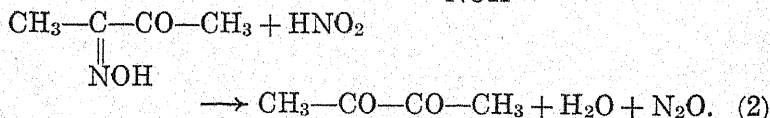
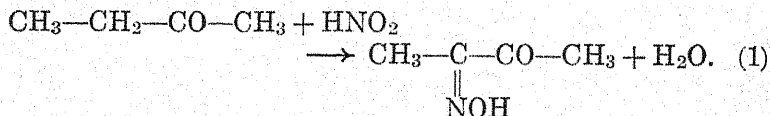
**Oximes.** An ether solution of benzaldoxime, when saturated with nitrogen trioxide, yields a crystalline precipitate of benzaldoxime peroxide. In contact with the ether solution of the oxides of nitrogen, it is further oxidized to benzildioxime peroxide:\*



Oximes and isonitroso compounds are converted into aldehydes or ketones by amyl nitrite or by any other source of nitrous acid:



Compounds having a methylene group adjacent to a carbonyl group are converted into isonitroso compounds by nitrous acid, and the isonitroso compounds are changed by an excess of the reagent to aldehydes or ketones. The two reactions, therefore, constitute an oxidation process. Diacetyl is made from methyl-ethyl ketone by treatment of the latter with nitrous acid:



\* Beckmann, *Ber.*, 22, 1591 (1889).



## REDUCTION

The reducing agents most frequently employed are hydrogen iodide, sodium amalgam, potassium alcoholate, hydrogen, hydrazine, sulfur dioxide, ammonium sulfide, ferrous sulfate, titanium trichloride, and stannous chloride. In connection with acids or alkalies, iron, zinc, tin, nickel, and other metals are frequently used. Metals are used also as catalysts in reductions with free hydrogen.\*

**Unsaturated carbon chains.** Unsaturated oils are hydrogenated by passing hydrogen gas through the hot oil, in which the catalyst is suspended. In this way triolein (from cottonseed oil) is converted into the solid tristearin (the chief component of beef and mutton fats). Rather and Reid applied the same principle in the reduction of unsaturated gases.† Freshly reduced nickel on the surface of fine particles of infusorial earth was suspended in molten paraffin (an inert medium) and a mixture of ethylene and hydrogen was passed through the suspension. The ethylene was reduced to ethane.

**Aldehydes and ketones.** Sodium amalgam is a convenient reagent for the reduction of an aldehyde or a ketone in aqueous or in alcoholic solutions. The time required for conversion of the carbonyl group to hydroxyl varies from an hour to two or three days, depending not only on the temperature, concentration of the solution, and thoroughness in stirring, but also upon the character of the aldehyde or ketone used.

To a solution of 10 g. of butyric aldehyde in 250 cc.  $\text{H}_2\text{O}$ , 1000 g. of 1 per cent sodium amalgam is added in 100-gram portions. The solution is stirred frequently, and kept slightly acid in reaction as long as hydrogen is being evolved. Butyl alcohol is obtained from the reaction mixture.

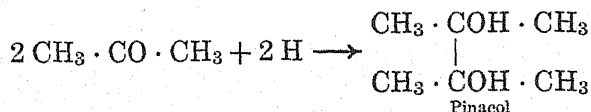
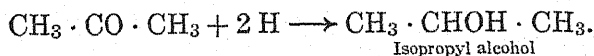
Reduction of a ketone may result in the formation of a tertiary alcohol or pinacol. Acetone, dissolved in ether which is saturated with water, is reduced by sodium; or, dissolved in water, it may be reduced by sodium amalgam. In either

\* Sabatier and Senderens, *La Catalyse de chimie*.

† Rather and Reid, *J. Am. Chem. Soc.*, **37**, 2115 (1915).



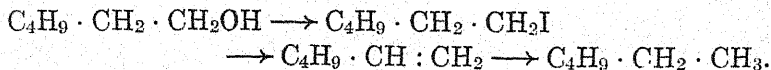
case two products, namely, isopropyl alcohol and pinacol, are formed :



The formation of pinacol is avoided by reducing the ketone with hydrogen gas in contact with hot finely divided nickel or copper. Pinacol becomes the principal product when acetone is reduced with magnesium in benzene. Mercuric chloride catalyzes the reaction. Magnesium pinacolate is the product actually formed in benzene solution, but the compound is easily hydrolyzed to pinacol and magnesium hydroxide.

Benzophenone is reduced by ethyl alcohol to benzpinacol when the solution is exposed to ultraviolet light.\* An equivalent quantity of alcohol is converted into acetaldehyde.

**Alcohols.** Some alcohols may be reduced to corresponding hydrocarbons by heating them with hydrogen iodide and red phosphorus. The reaction is not a general one. The first step in the process consists in replacement of the hydroxyl group by iodine, and with many alcohols the action stops at that point. In other cases hydrogen iodide is eliminated from the saturated halogen derivative, leaving an unsaturated hydrocarbon. The latter is usually reduced further by the same reagents, yielding a saturated hydrocarbon and iodine.

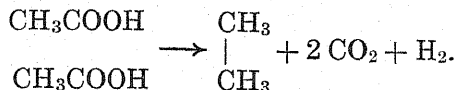


Tertiary alcohols, and especially those of the aromatic series, are very easily reduced; thus triphenyl carbinol is converted, almost quantitatively, into triphenylmethane by zinc and warm acetic acid. The reaction is completed within two or three hours.

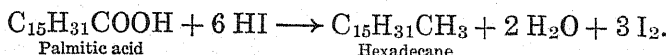
**Acids.** Some acids are converted into primary alcohols by electrolytic reduction. This reaction is not a general one. Many acids yield hydrocarbons when subjected to electrolysis.

\* Porter, Ramsperger, and Steel, *J. Am. Chem. Soc.*, 45, 1830 (1923).

Acetic acid, for example, yields ethane, carbon dioxide, and hydrogen:



A few of the higher members of the acetic acid series and some homologues of benzoic acid have been reduced to hydrocarbons by heating them in sealed tubes four or five hours with hydriodic acid and red phosphorus at temperatures between 200° C. and 240° C.



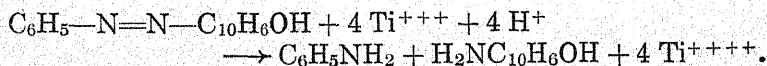
In general, the direct reduction of the carboxyl group is not a practical operation. It is much easier to reduce acid anhydrides, esters, and acid chlorides. Consequently it is a common practice to convert the acid into one of these derivatives as a preliminary step.

Aliphatic esters and esters of aromatic acids in which the carboxyl group is not attached directly to the ring are readily reduced to alcohols by treatment with absolute ethyl alcohol and metallic sodium. Acid chlorides are reduced to alcohols and amides to amines by the Sabatier and Senderens catalytic process described on pages 383 and 384.

**Nitriles.** The alkyl cyanides, or nitriles, are only slightly soluble in water but quite soluble in alcohol. The latter is therefore used as a solvent, and reduction is accomplished by the addition of metallic sodium. The solution is boiled under a reflux condenser and sodium is added from time to time. After about four times the calculated quantity of sodium has been dissolved the mixture is acidified and the solvent is distilled off in vacuo. The free amine is then released by addition of alkali and obtained by distillation or by extraction with ether:



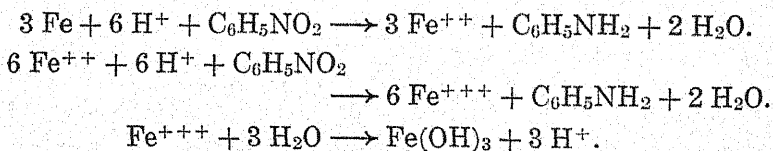
**Azo compounds.** The azo dyes are reduced quantitatively by titanous chloride. A standardized solution may be used to titrate an aqueous or alcoholic solution of an azo dye, the disappearance of color indicating the end point. The molecules are broken between the nitrogen atoms of the azo group:



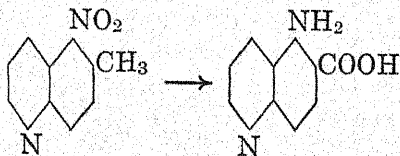
Phenyhydrazones break in the same way when treated with sodium amalgam and dilute acetic acid. The hydrazone is dissolved or suspended in ten to fifteen times its weight of 90 per cent alcohol, then shaken with an excess of 2 per cent sodium amalgam. Acetic acid is added from time to time in sufficient quantities to give the mixture a slightly acid reaction.

**Nitro compounds.** Aromatic nitro compounds may be converted into amines by a great variety of reagents in either acid or alkaline solutions. An exhaustive study of the mechanism of the change and the influence of the environment upon the types of intermediate products formed was made by Haber, who reduced nitrobenzene electrolytically in acid, alkaline, and nearly neutral solutions. By varying the current density, he was able to produce effects comparable to the results obtainable with weak or strong reducing agents. His results are incorporated in the discussion of nitrobenzene.

In the commercial process of making aniline, iron and hydrochloric acid are used to reduce nitrobenzene. Very little hydrochloric acid is required, a sufficient concentration of hydrogen ions being provided by the hydrolysis of ferric ions. The function of the iron as a reducing agent is shown in the following equations. These equations, however, do not show all the steps involved in the process.



Reduction of an aromatic nitro group with simultaneous oxidation of a side chain in the same molecule has been accomplished through the agency of an alcoholic solution of potassium hydroxide. In this way Bogert and Fisher prepared an aminoquinoline carboxylic acid from 5-nitro-6-methylquinoline:



In the same way *ortho*-nitrotoluene is converted into anthranilic acid.

**Other reductions.** An alkyl halide may be reduced to a hydrocarbon by passing its vapor, mixed with water vapor, over zinc at  $150^{\circ}$ – $170^{\circ}$ . Or, if dissolved in alcohol containing water, it may be reduced by boiling with zinc dust. This treatment always results in the formation of mixed products. Thus ethyl iodide yields butane along with ethane. Aromatic halogen compounds behave the same way. Diphenyl,  $\text{C}_6\text{H}_5\cdot\text{C}_6\text{H}_5$ , is regularly formed in the preparation of phenyl magnesium iodide (Grignard reagent) by the action of magnesium on phenyl iodide,  $\text{C}_6\text{H}_5\text{I}$ , in ether.

An alcoholic solution of an alkyl halide, if heated with sodium, usually yields an unsaturated hydrocarbon if the structure of the alkyl halide permits the removal of hydrogen and halogen from adjacent carbon atoms.

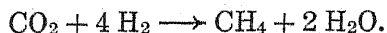
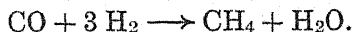
A process of reduction by hydrogen under the catalytic influence of a finely divided metal was developed by Sabatier and Senderens between 1897 and 1912, and since then many modifications of the reaction have been worked out.

The reaction is carried out by passing a mixture of hydrogen and the vapor of the substance to be reduced over freshly reduced nickel, cobalt, copper, or iron in a heated tube. The temperature required varies with the type of compound to be reduced. Some reductions proceed smoothly and rapidly at  $30^{\circ}$ – $40^{\circ}$ , whereas other compounds must be heated to  $250^{\circ}$ – $300^{\circ}$ . By far the most efficient catalyst for most reductions is nickel. It is prepared by saturating lumps of pumice stone with a solution of nickel nitrate and heating the mass to convert the nitrate into an oxide. The pumice is then placed in a hard glass tube and heated to  $320^{\circ}$ – $350^{\circ}$  with a stream of hydrogen passing through it. The oxide is reduced to metallic nickel. The material is not removed, but is used at once as a catalyst for gas reactions in the same tube.

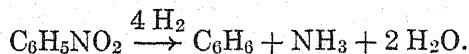
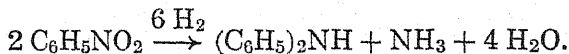
Ethylene and hydrogen, in the presence of nickel, form ethane at temperatures as low as  $30^{\circ}$ – $35^{\circ}$ . At  $150^{\circ}$  the reaction is rapid. Above  $300^{\circ}$  there is considerable decomposition of ethylene, resulting in deposition of carbon.

Acetylene and hydrogen combine at ordinary temperatures with an evolution of heat that may spontaneously raise the temperature of the contents of the tube to  $150^{\circ}$ . Ethane is the principal product, but small quantities of aromatic and hydroaromatic compounds are formed.

Carbon monoxide and carbon dioxide are reduced by hydrogen in the presence of nickel at 230°-250°. The reaction proceeds slowly at 180°:



Aliphatic and aromatic nitro compounds yield primary amines. Secondary and tertiary amines appear in smaller quantities; hydrocarbons and ammonia also are among the by-products:

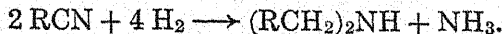
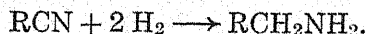


At temperatures above 300° the benzene ring is ruptured and methane, ammonia, and water constitute the principal products.

Phenols are reduced to hydrocarbons. The reaction is slow and incomplete at 250°, and at higher temperatures there is considerable decomposition, giving rise to methane and other aliphatic bodies.

Alkyl and aryl chlorides are similarly reduced. Nickel chloride is formed during the reaction but is reconverted to metallic nickel by the excess of hydrogen. Bromides and iodides also yield hydrocarbons, but the reaction is less successful than with chlorides, probably because of the fact that nickel chloride is more readily reduced than is the bromide or iodide.

Cyanides yield amines. Primary amines predominate in the products formed, but secondary and tertiary amines and ammonia are always present:



## CONJUGATION AND RESONANCE

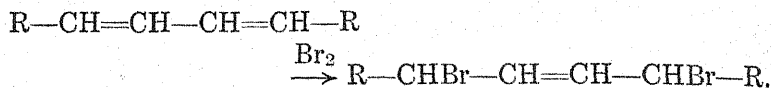
**Kopp's law.** In 1855 Kopp advanced the idea that the properties of compounds are additive functions of the properties of the individual groups or bonds which comprise the molecule.\* It was assumed that each bond and each characteristic group in a molecule contributes a definite amount to the numerical values of the physical constants relating to the molecule. More or less successful attempts were made to calculate heats of combustion, absorption spectra, indices of refraction, magnetic rotations, and other properties of compounds by adding together appropriate values for the various bonds or atomic groups in a molecule.

It soon became apparent, however, that Kopp's law gave only rough approximations to the true values of physical constants, and that the character of every bond in a chemical compound is changed or modified by every change in the configuration of the molecule and by every substitution of one atom or group for another in any part of the molecule. In many saturated systems the deviations from Kopp's law are relatively small, but in unsaturated systems the deviations are usually very great. A study of the properties of unsaturated compounds leads to the conclusion that their structures are not adequately represented by formulas containing only the ordinary single, double, and triple bonds.

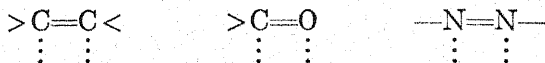
It was observed as early as 1880 that the character of a double bond may be modified by the presence of another double bond in the molecule and that the type of addition product formed by a compound containing two or more double bonds is dependent upon the relative positions of these multiple linkages. In most cases an addition involving a diolefin is accomplished by breaking a double bond, an ion or radical of the addendum becoming attached to each of the two atoms originally connected by the double bond. There are many cases, however, in

\* H. Kopp, *Ann.*, 96, 155, 303 (1855).

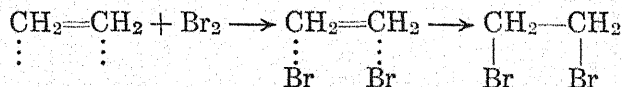
which double bonds are broken with addition to atoms that are not adjacent. Bromine, for example, acts upon a 1, 3-diene as follows:



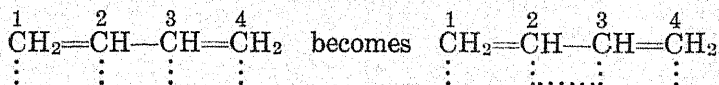
To account for anomalies of this kind Thiele advanced a theory of partial valence, which has been quite useful in the classification of addition reactions. Thiele maintained that when atoms are joined by double or triple bonds there is free or unused residual valence on each of the atoms so connected. This partial or residual valence he represented by dotted lines as follows:



According to this view, unsaturated compounds are reactive because of the free partial valences. Addition takes place on these free partial valences, and the full force of a single bond is then established in the new linkage at the expense of the double bond. Thus the reaction between ethylene and bromine is

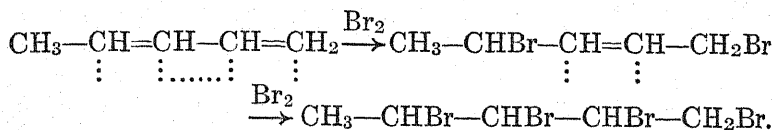


**Conjugated systems.** A compound having a pair of double bonds separated by a single bond is referred to as a conjugated system. In such cases the partial or residual valences on atoms that are linked together by single bonds may partially satisfy each other and become relatively inactive:

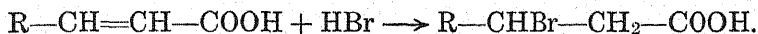


Carbon atoms 1 and 4 remain active, but the valence requirements of carbon atoms 2 and 3 are to a considerable extent mutually satisfied. In a compound of this type, 1, 4 addition occurs. Carbon atoms 1 and 4 thus become saturated, but 2 and 3 are still unsaturated and a double bond is established in the 2, 3 position. Conjugation is then impossible, and the next addi-

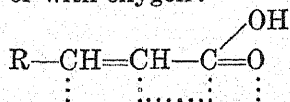
tion occurs on carbon atoms 2 and 3. Thus the saturation of 1, 3-pentadiene by bromine proceeds in steps as follows :



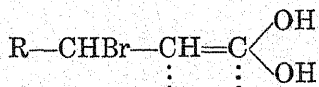
It was stated in an earlier chapter that when polar compounds, such as the halogen acids, are added to unsaturated compounds, the negative ion usually becomes attached to the carbon atom that is holding fewest hydrogen atoms. Thus hydrogen bromide acts upon propylene,  $\text{CH}_3-\text{CH}=\text{CH}_2$ , forming isopropyl bromide,  $\text{CH}_3-\text{CHBr}-\text{CH}_3$ . Contrary to this rule, hydrogen bromide acts upon acrylic acid,  $\text{CH}_2=\text{CH}-\text{COOH}$ , forming  $\beta$ -bromopropionic acid,  $\text{CH}_2\text{Br}-\text{CH}_2-\text{COOH}$ . All  $\alpha$ - $\beta$ -unsaturated acids react with hydrogen bromide in the same way, that is, they yield  $\beta$ -halogen acids :



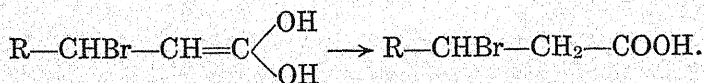
Thiele's theory affords an explanation. If the bromine had equal chances for combination with the two unsaturated carbon atoms, mixed products would be obtained ; but the acid presents a conjugated system in which the  $\alpha$ -carbon is inactive. The choice presented to the bromine atom is that of combining with the  $\beta$ -carbon atom or with oxygen :



Under such circumstances the bromine attaches to the  $\beta$ -carbon atom, the more positive hydrogen going to the oxygen :

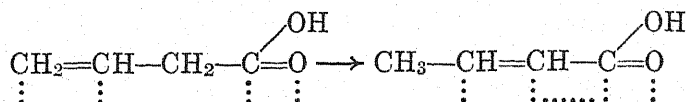


One of the hydroxyl hydrogen atoms then migrates to the  $\alpha$ -carbon, regenerating the carboxyl group :

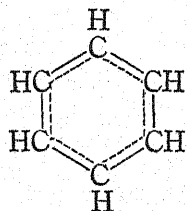




The shift of the position of the double bond when a  $\beta$ - $\gamma$ -unsaturated acid is heated with an alkali was explained by Thiele as due to a tendency to reduce as far as possible the residual valence in such a compound. A conjugated system is more nearly saturated than one having the same number of double bonds in positions that preclude the possibility of conjugation. A shift of the double bond from the  $\beta$ - $\gamma$  to the  $\alpha$ - $\beta$  position reduces the free partial valences from four to two:



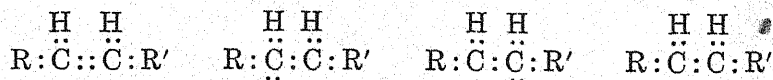
Conjugation is defined as an interaction between two or more groups in the same molecule. This interaction results in increased stability, large deviations in physical properties from those predicted by Kopp's law, and markedly greater or lessened chemical reactivity as compared with the reactivities of substances in which conjugation does not occur.



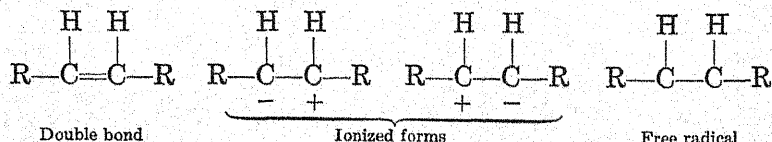
Thiele's formula  
for benzene

Conjugation accounts for many peculiar phenomena in the aromatic series as well as in the aliphatic group. Benzene, for example, displays a completely conjugated system, and in consequence of this it acts more like a saturated than an unsaturated compound. It adds chlorine and bromine only very slowly in spite of the formal possession of three double bonds.

**Resonance.** We may represent the possible structures of an ethylenic system by the following electron distributions:



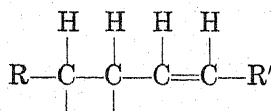
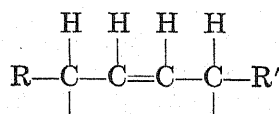
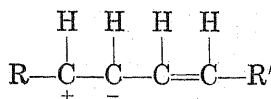
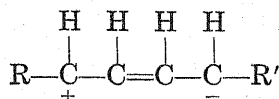
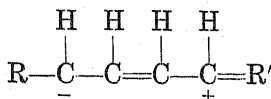
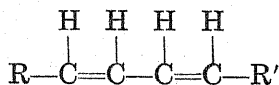
These structures in the older type of formula appear as follows:



We shall generally use a line to represent a pair of shared electrons, a double bond for two pairs, and a triple bond for three

pairs of shared electrons, instead of employing dots to show electron distributions.

Two double bonds in conjugated positions give rise to many forms, including the following :

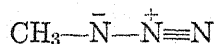
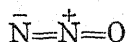


It is obvious that, without shifting atomic centers, the electronic arrangements may be quite varied. The simple diene formulations cannot be quite correct; the actual molecule is a composite of all these. It does not correspond exactly to any one of these forms, but is capable of reacting as if it were any one of them. This point of view does not imply that the compound is necessarily a tautomeric mixture of all forms in a state of equilibrium; rather, we should assume that the actual molecule has none of these structures, but is in a form more stable than any single representation of this kind. The exact structure of the molecule is inexpressible in terms of bonds alone, nor can we, on the basis of present knowledge, assign a single definite electronic configuration to the molecule. The actual structure, whatever it may be, is called a *resonated structure*. Like a tautomeric mixture, it has the capacity to react as if it were any of the possible forms.

Resonance may be defined as interactions between two or more electronic structures of the same molecule. The period of oscillation between possible forms is believed to be of the order of  $10^{-15}$  seconds. To obtain resonance the various possible electronic structures must not differ greatly in energy content. The atoms (atomic nuclei) do not change position with respect to each other in the process of resonance. The phenomenon involves changes in electronic configurations only. Unlike a tau-

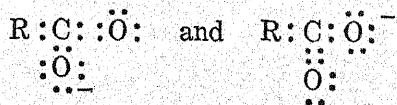
tomeric mixture, the resonated structure has a higher heat of formation than the calculated value for *any* of the limiting forms.

As evidence that oscillation of the electronic charges between the limiting forms in a resonating molecule is very rapid, the fact may be cited that the dipole moments of nitrous oxide and organic azides are very small, whereas the structures



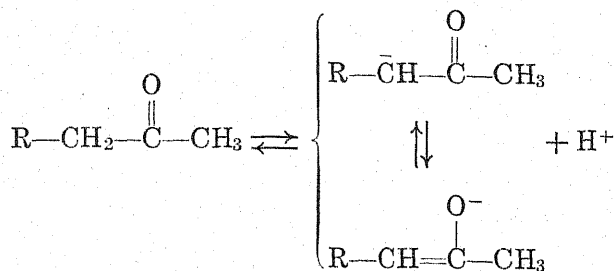
would lead to high moments if the shift from one form to the other were slow as compared with the time of relaxation ( $10^{-12}$  sec.) of the molecule in an electrical field. Since resonance is considered to have a period of about  $10^{-15}$  seconds, each of these compounds should be represented by an intermediate structure in which there is no wide separation of charges. Comparatively few molecules would ever be in either of the extreme forms represented by the above formulas. Resonance is a stabilizing influence, equivalent to any other method of decreasing the free energy of a system.

The formula  $\text{R}-\text{C}\begin{smallmatrix} \text{O}^- \\ \text{O} \end{smallmatrix}$  does not accurately represent the structure of the anion of an organic acid. According to this formula the two oxygen atoms are not equivalent. One of the oxygen atoms is associated with a negative charge and the other is shown as doubly linked to the carbon atom. No such difference in character is detectable by any chemical or physical method. An acid ion exists in a resonated form in which the two oxygen atoms are exactly equivalent. The extreme limits through which the electrons may move are shown in the following structures, but the resonated form (the structure that accurately pictures the vast majority of the ions) corresponds to an electronic configuration that lies between these extreme forms. In very few ions will the oscillations have amplitudes as great as are represented in these limiting structures.



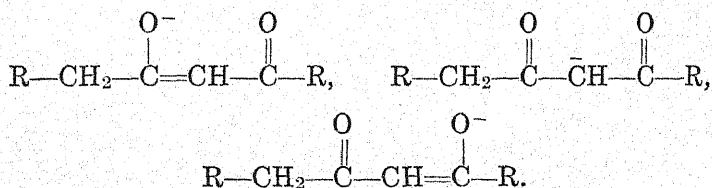
Resonance occurs in the ion to a much greater extent than in the undissociated molecule, and this stabilizing influence promotes dissociation of the acid.

A similar argument applies with respect to the mobility of hydrogen on the  $\alpha$ -carbon atom in a ketone.

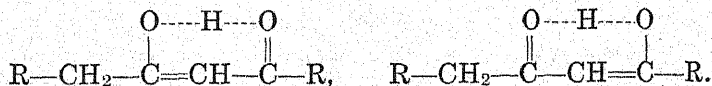


Resonance between the two forms of the ion stabilizes the ionic structure and promotes the release of the  $\alpha$ -hydrogen atom. In 1, 3-diketones the multiplicity of forms greatly stabilizes the

ion and the enol as well. The ketone  $\text{R}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}$  is in equilibrium with the enol,  $\text{R}-\text{CH}_2-\overset{\text{OH}}{\parallel}{\text{C}}=\text{CH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}$ . The enol ionizes, and the ion is a resonating structure capable of existing in many forms, including the following :



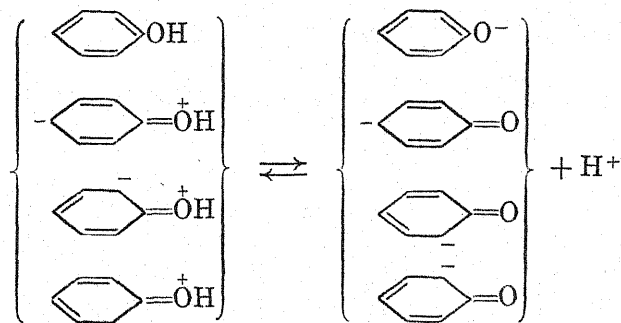
Resonance in the un-ionized enol gives rise to chelate structures of the following type:



In these formulas the hydrogen atom is shown attached to both oxygen atoms. We speak of the oxygen atoms as being connected through a "hydrogen bond," and the cyclic structure produced through the hydrogen bond is called a chelate com-

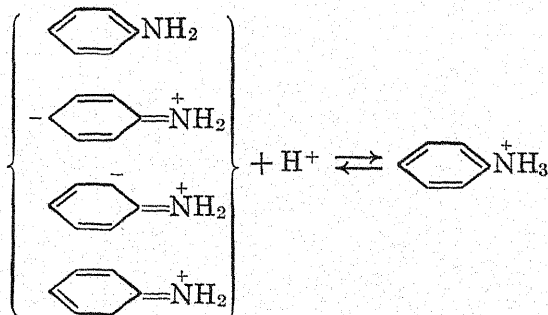
pound. A hydrogen bond can be established in a case of this kind because in the cyclic form both oxygen atoms are within bonding distance of the hydrogen atom.

Closely related to the aliphatic keto-enol problem is resonance in aromatic systems. Two phenomena may be considered here: (a) the acidity of phenols and (b) the weak basicity of aromatic amines. In the case of the former, we may represent the dissociation as follows:



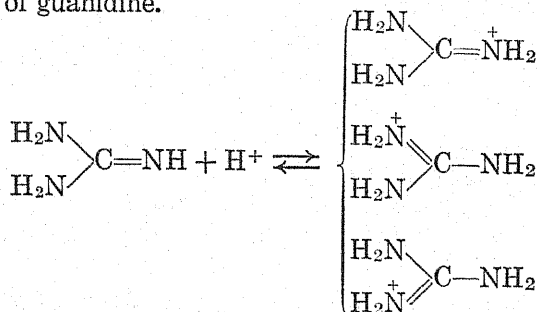
Resonating structures are written for both the undissociated phenol and the anion; but the resonance energy of the ion far exceeds that of the phenol itself, and this favors dissociation. This explains the high acidity of a phenol as compared with that of an alcohol, in which no resonance occurs.

In the case of an amine, resonance favors formation of the free base.



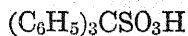
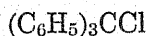
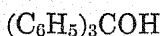
In the salt no resonance is possible. Resonance stabilizes the free base and explains the low dissociation constant of aniline ( $4.6 \times 10^{-10}$ ) as compared with that of ammonia ( $1.8 \times 10^{-5}$ ).

Resonance plays an enormous role in determining the base strength of guanidine.



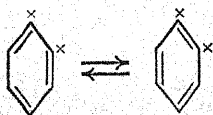
There are three equivalent forms of the cation derived from a guanidine salt. The three forms are identical in structure and in energy content, and this equivalence favors resonance in the ion. Resonance is possible in the free base, but no other possible form of the free base has as low an energy content as the one shown above. The difference in the resonating capacities of free guanidine and the ion favors the production of ions (salt formation), and guanidine acts like a strong base.

The same factors participate in determining the dissociation of negative groups, such as hydroxyl, halogen, and the sulfonic acid group, from arylated methane derivatives. The simple aliphatic compounds, ROH, RCl, and RSO<sub>3</sub>H, show no tendency to ionize, and all reactions involving the rupture of the C—O, C—Cl, and C—S bonds in these compounds are slow. The same groupings, however, in such compounds as



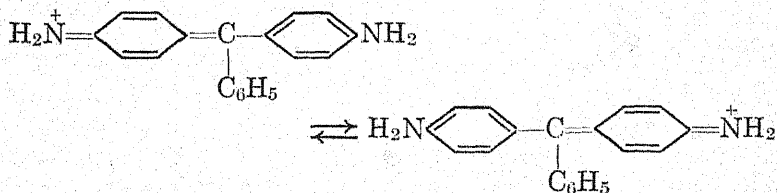
either actually ionize or are extremely reactive. The marked difference may be ascribed to the capacity of the aromatic ring systems to absorb the positive charge through resonance.

The problem of the structures of benzene, naphthalene, and anthracene may be answered in terms of resonance. The failure to find isomeric *ortho*-disubstitution products of benzene demands a labile structure for the benzene ring. The two interchanging Kekulé structures



suffice to explain the fact if we assume that the isomeric change is rapid as compared with any known method of separating the isomers. On the basis of Kopp's law the heat of combustion of benzene should be about 37,000 calories greater than that found. Neither of the above structures, carrying all the implications of aliphatic chemistry, accounts for the great stability of benzene nor for its slight tendency to form addition products, nor for its low heat of combustion. It is believed, therefore, that neither formula is correct, but that the actual molecule is the result of interaction between these two; that is, it is a resonated form.

The production of absorption bands in the visible spectrum is accompanied by an extended conjugated or resonating system. Thus in derivatives of triphenylmethane the resonance normally involves two rings when color is produced. An example is phenolphthalein (page 281), which is not colored until, through ionization of the second phenol group, the two rings are rendered identical from a resonance standpoint. Similarly salts of mono-aminotriphenylcarbinol are not colored, but the diamino and triamino derivatives are colored. Resonance occurs in salts of the diamino compounds as follows:



**Resonance and bond distances.** Intramolecular attraction as well as intermolecular attraction tends to reduce the distance between atomic centers. In saturated compounds the distance between carbon atoms (the C—C bond) is 1.54Å. When doubly linked (the C=C bond) the distance becomes 1.35Å, and in acetylene (the C≡C bond) the distance is 1.15Å. In benzene the carbon atoms are equidistant from each other and 1.42Å apart. The distance between two atoms that are linked through a single bond is modified by the presence of an adjacent double bond. This is shown by comparing the C—Cl bond distances in phenyl chloride, vinyl chloride, and ethyl chloride. The distances are 1.70Å, 1.68Å, and 1.76Å respectively. Conversely, deviations from normal bond distances become a measure of the degree of resonance.

## CONDENSATION PROCESSES \*

### THE GRIGNARD REACTION

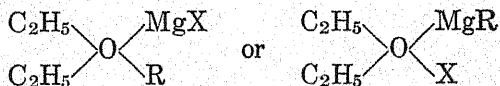
In the year 1901, Grignard † published the results of his experiments on the preparation of alkyl magnesium halides and their applications in synthetic processes. His work led to the development of one of the most important general reactions in the field of organic chemistry.

**The Grignard reagent.** A weighed quantity of clean, dry magnesium turnings is suspended in pure dry ethyl ether in a flask provided with a reflux condenser. An anhydrous ether solution of an alkyl or aryl halide (containing a quantity of the compound chemically equivalent to the weight of magnesium) is added. A crystal of iodine is sometimes used as a catalyst, but the reaction usually begins at once without a catalyst and becomes violent if not retarded by cooling. Heat is evolved and the ether boils vigorously. If it fails to boil spontaneously, the mixture is warmed on a water bath until the magnesium is dissolved. The reaction between magnesium and the alkyl halide is represented by the equation



The product  $RMgX$  is known as the Grignard reagent.

In consideration of the fact that the reagent generally retains one molecule of ether when the solution is evaporated to dryness, many investigators have assumed that it should be considered an oxonium compound of the type



\* Cohen defines condensation as "the union of two or more organic molecules or parts of the same molecule, with or without elimination of component elements, in which the new combination is effected between carbon atoms." The term, therefore, applies to a great variety of synthetic processes. Typical examples of condensation are Wurtz's synthesis, Perkin's synthesis, the Grignard reaction, the Friedel and Crafts reaction, and so on.

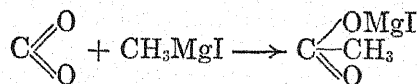
† Grignard, *Ann. chim. et phys.*, 7th series, 24, 433 (1901). For a good bibliography of the Grignard reaction see West and Gilman's "Organo-magnesium Compounds," *National Research Council Reprint No. 24* (1922).



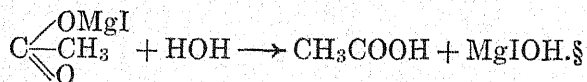
Other support for this conclusion is based upon the fact that magnesium is not attacked by alkyl halides in the presence of such solvents as benzene, toluene, and the paraffin hydrocarbons. The reagent can be prepared, however, in benzene-ether mixtures containing much less ether than the quantity theoretically required to produce the oxonium compound\*; or it may be prepared in the absence of any oxygen compound, as, for example, in dimethylaniline† or in quinoline.‡ It is true that the solvent is held more or less firmly by the organo-magnesium compound, but it is equally certain that the solvent may be removed until the quantity remaining falls far below the limits demanded by the oxonium formula. In fact some alkyl magnesium halides have been prepared by the action of the metal and the alkyl halide in the absence of any other substance.

Side reactions reduce the yields of organo-magnesium compounds. The most important deviation from the main reaction is due to the tendency of magnesium to act upon alkyl halides with the formation of magnesium halide and hydrocarbons. With potassium, sodium, or even with zinc, instead of magnesium, this is the normal course taken (Wurtz's synthesis).

**Carbon dioxide.** When a stream of carbon dioxide is passed into an ether solution of methyl magnesium iodide, a crystalline addition product is formed at once:



The ether solution is poured upon crushed ice to hydrolyze the addition product, and hydrochloric or sulfuric acid is added to prevent precipitation of magnesium hydroxide. Acetic acid is formed in this reaction:



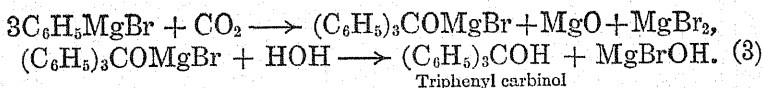
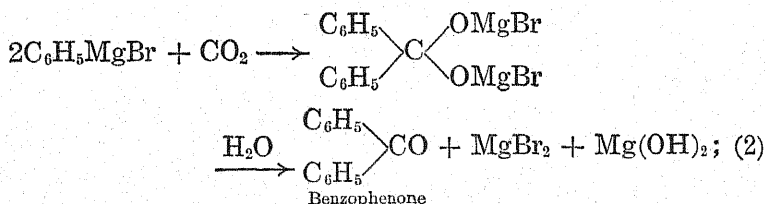
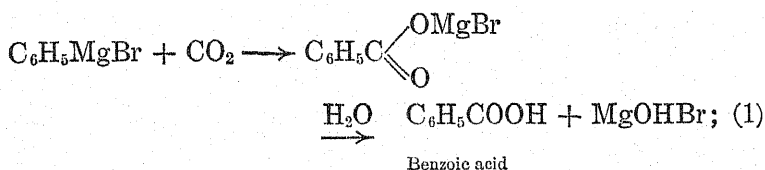
\* Tschelinzeff, *Ber.*, **37**, 4534 (1904).

† Tschelinzeff, *ibid.*, 2081.

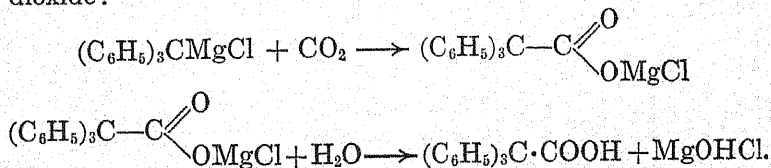
‡ Sachs and Sachs, *Ber.*, **37**, 3089 (1904).

§ In the acid solution the salt MgIOH does not exist. The products are MgI<sub>2</sub>, MgCl<sub>2</sub>, or MgSO<sub>4</sub>, or the ions of these salts. In order to keep the equations in the simplest possible forms we shall use formulas of the type MgXOH to represent hydrolysis products of compounds formed through reactions of the Grignard reagent.

Homologues of acetic acid may be prepared in the same way by substituting for the methyl group any other alkyl radical. Benzoic acid and its homologues may be prepared with equal ease by using aryl magnesium halides. The influence of the halogen, though usually slight, cannot be ignored. In this case it is quite an important factor. Magnesium phenyl iodide with carbon dioxide gives a good yield of benzoic acid.\* The corresponding bromide yields very little benzoic acid, the principal products being triphenyl carbinol and benzophenone. The three products are formed simultaneously under any circumstances, but any one of them may be made to predominate by suitably modifying the conditions of the experiment :



A quantitative yield of triphenylacetic acid is obtained when triphenylmethyl magnesium chloride is treated with carbon dioxide:

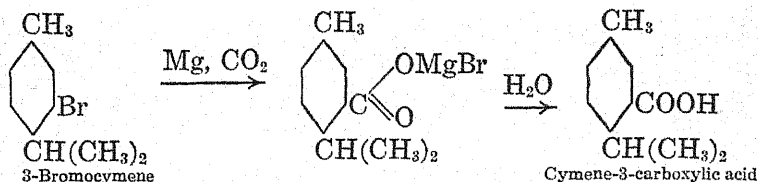


The cymene carboxylic acids are made from the corresponding bromides by means of the Grignard reaction.† A few drops

\* Zelinsky, *Ber.*, **35**, 2687 (1902).

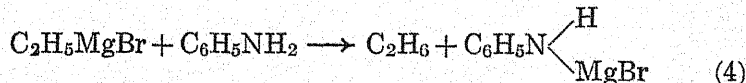
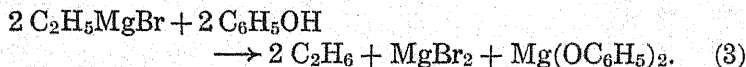
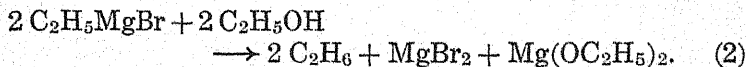
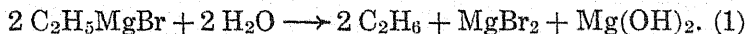
† Bogert and Tuttle, *J. Am. Chem. Soc.*, **33**, 1853 (1916).

of ethyl iodide activate the magnesium so that it dissolves rapidly in an ether solution of bromocymene. The ether solution is then cooled to about  $-10^{\circ}$  and kept in contact with carbon dioxide under pressure for eight or ten hours. The product is hydrolyzed with ice and dilute hydrochloric acid:



Sulfur dioxide,\* nitrogen dioxide,† and carbon disulfide combine with the Grignard reagent, forming compounds analogous to those formed with carbon dioxide.

Water, alcohols, phenols, and amines decompose alkyl and aryl magnesium halides, with the formation of hydrocarbons, as indicated by the following equations:



Amino and hydroxyl hydrogen may be estimated quantitatively by measuring the ethane gas evolved in these reactions.‡

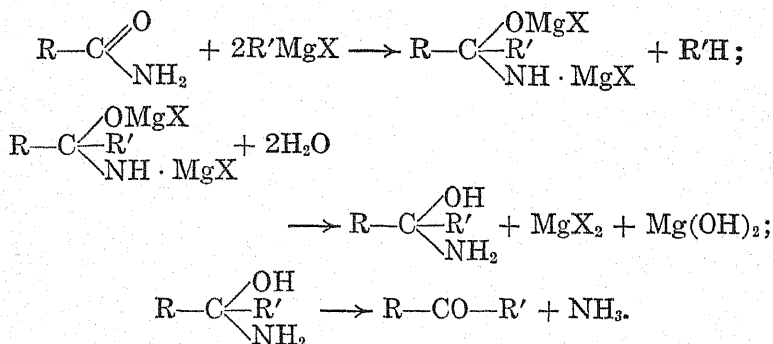
Primary amines are capable of further action. Both amino hydrogen atoms are removed at elevated temperatures (boiling point of the ether solution). A secondary amine, having only one available hydrogen atom, reacts with but one molecule of the reagent. Tertiary amines are inactive. The metallic derivatives formed in these reactions are hydrolyzed rapidly by water, regenerating the original amines, phenols, and alcohols. The carbonyl as well as the amido group in an amide is

\* Rosenheim and Singer, *Ber.*, 37, 2152 (1904). Houben and Kesselkaul, *Ber.*, 35, 3695 (1902).

† Wieland, *Ber.*, 36, 2315 (1903).

‡ Hibbert and Sudborough, *Proc. Chem. Soc.*, 19, 285 (1903).

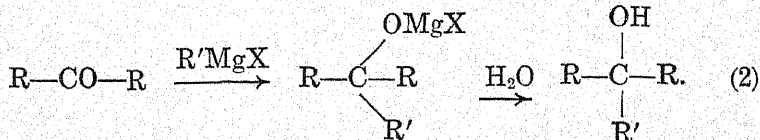
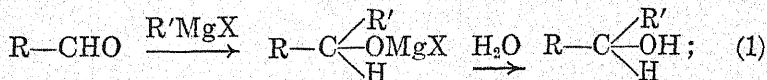
susceptible to reaction with alkyl magnesium halides. A ketone is the final hydrolysis product derived from a primary amide, but the yield is unsatisfactory:



The last step takes place spontaneously at temperatures attained on a water bath.

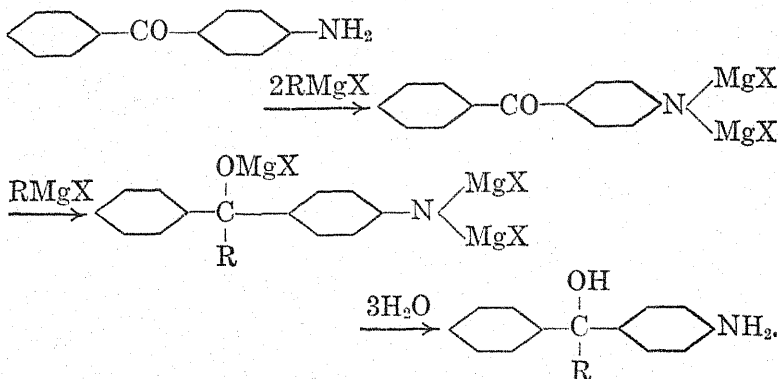
**Aldehydes and ketones.** The Grignard reagent acts upon aldehydes and ketones, forming compounds which are readily hydrolyzed to alcohols. Generally an ether solution or suspension of the aldehyde is added to an ether solution of the reagent, and the mixture is warmed on a steam bath under a reflux condenser for two or three hours. The reaction mixture is then cooled and slowly poured on cracked ice. The hydrolysis is accompanied by the evolution of heat. Enough hydrochloric acid or ammonium chloride is added to the ice to hold the magnesium in solution, and the alcohol is extracted with ether.

Formaldehyde gives rise to primary alcohols. All other aldehydes yield secondary alcohols, and ketones are converted into tertiary alcohols:

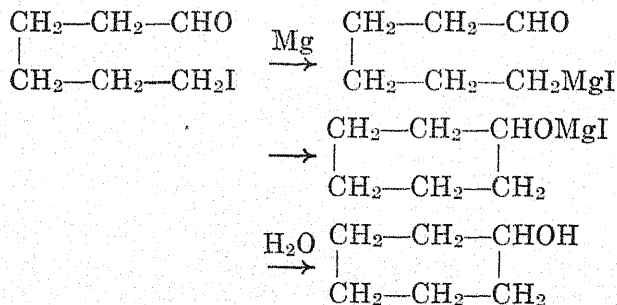


If the aldehyde or ketone is also a primary or secondary amine, an excess of the reagent must be used, for the speed of

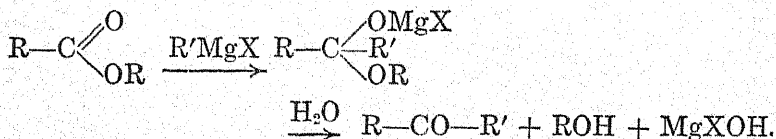
the reaction with an amino group is much greater than with the carbonyl. The latter reacts, therefore, only with the magnesium compound remaining after the amino group has been completely satisfied. With aminobenzophenone, for example, the reactions proceed as follows: \*



Cyclic compounds have been made by the action of magnesium on ether solutions of halogen-substituted aldehydes and ketones.†



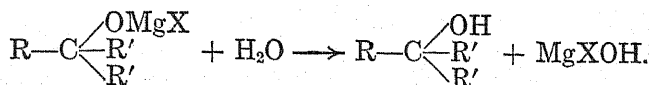
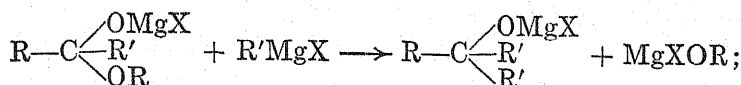
**Acid chlorides and esters.** With acid chlorides and esters, the aryl and alkyl magnesium halides form addition products which, upon hydrolysis, yield ketones or tertiary alcohols:



\* Porter and Hirst, *J. Am. Chem. Soc.*, 41, 1264 (1919).

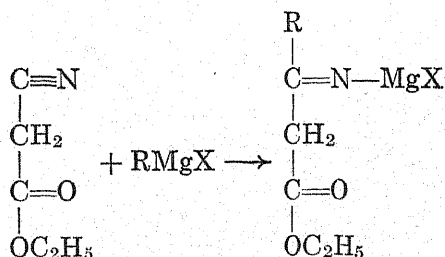
† Zelinsky and Moser, *Ber.*, 35, 2684 (1902).

With an excess of the reagent the alkoxyl group of the ester is replaced by an aryl or alkyl radical:



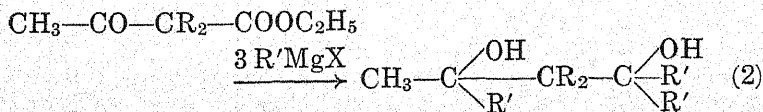
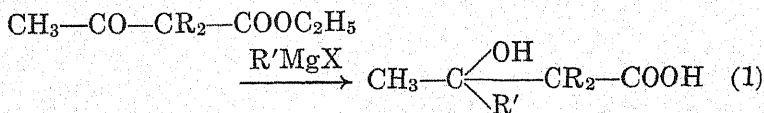
Esters of formic acid yield aldehydes or secondary alcohols. The production of benzaldehyde from ethyl formate and phenyl magnesium bromide is accomplished on a commercial scale.

Many esters are capable of reacting in more than one way. In cyanoacetic ester, for example, the cyanide radical or the carbonyl or both may unite with the reagent. The product formed depends upon the relative velocities of the possible reactions. In this case the fastest action is addition on the  $-\text{CN}$  group:

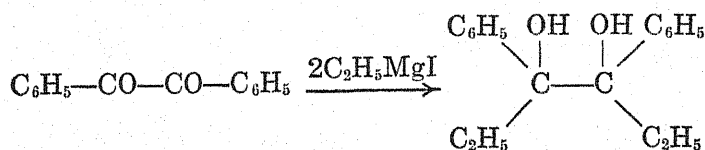


On hydrolysis this product yields a  $\beta$ -ketonic ester.

When treated with a Grignard reagent, acetoacetic ester and other  $\beta$ -ketonic esters which are capable of tautomeric change react in the enol form. The original ester is regenerated when the reaction product is hydrolyzed with cold water. On the other hand, dialkyl acetoacetic esters yield  $\beta$ -hydroxy acids and ditertiary alcohols:

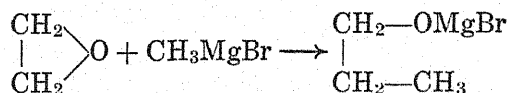


Ditertiary alcohols have been obtained also from diketones. Thus benzil has been converted into diphenyldiethyl glycol:



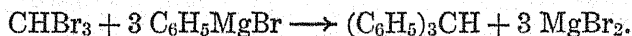
Since many tertiary alcohols lose water and form unsaturated hydrocarbons when heated, the Grignard reaction has been used to prepare derivatives of ethylene.

**Alkylene oxides.** Ethylene oxide and propylene oxide form addition products with alkyl magnesium halides:

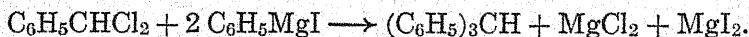


On hydrolysis the addition product is converted into a primary alcohol.

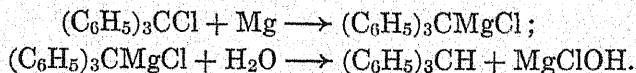
**Halogen compounds.** Chloroform and bromoform react energetically with the Grignard reagent, yielding products in which one or more of the halogen atoms are replaced by hydrocarbon radicals. Triphenylmethane is produced by this reaction:



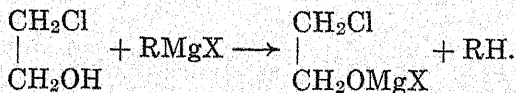
Benzal chloride yields its chlorine in a similar way, giving the same product:



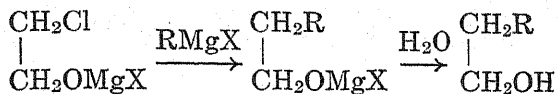
Halogens may be replaced by hydrogen, by converting the halide into a magnesium addition product, then decomposing the compound with water. Triphenylchloromethane is thus converted into triphenylmethane:



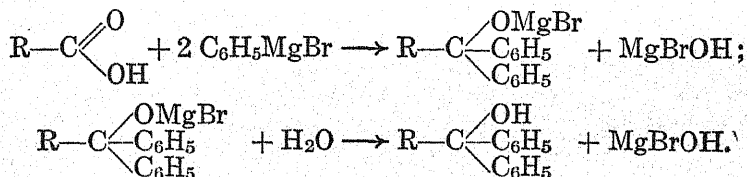
With ethylene chlorohydrin and its homologues an alkyl or aryl magnesium halide acts first with the hydroxyl group:



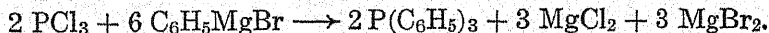
If an excess of the reagent is used, the chlorine atom is replaced by a carbon radical:



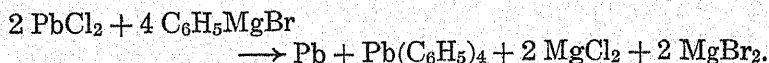
**Organic acids.** Monobasic aliphatic acids, also benzoic acid and its homologues, are converted into tertiary alcohols by dissolving or suspending them in dry ether with phenyl magnesium bromide, and boiling the mixtures from one to six hours.\* Although dry acids and a nonionizing solvent are used in this process, the first step in each case is a replacement of the hydrogen atom in the carboxyl group. Hydrocarbons appear as by-products of the reaction. The following equations, therefore, show only in a qualitative way how alcohols may be obtained from acids. The dibasic acids (oxalic, malonic, succinic, and adipic) fail to yield analogous products.



**Inorganic salts.** The halogen salts of mercury, lead, tin, arsenic, antimony, bismuth, silicon, phosphorus, and thallium are decomposed by alkyl and aryl magnesium halides with the formation of organic derivatives of these elements. Phosphorus trichloride, with an excess of phenyl magnesium bromide, yields triphenylphosphine:



Mercury biphenyl, tin tetraphenyl, and trimethylarsine are formed with equal ease. The behavior of lead chloride is of interest, a tetra-aryl derivative being produced from a salt in which the lead atom is bivalent:

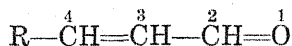


Lead tetraphenyl crystallizes in colorless prisms melting at 227.7°.

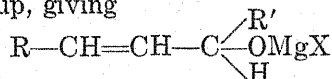
\* F. N. Peters, Jr., Esther Griffith, D. R. Briggs, and H. E. French, *J. Am. Chem. Soc.*, 47, 449 (1925).



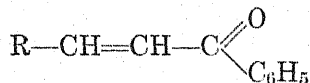
**Unsaturated compounds.** Kohler and his coworkers have discovered certain regularities in the addition of the Grignard reagent to unsaturated compounds presenting conjugate systems of double bonds.\* Aldehydes of the type



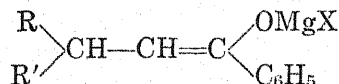
yield 1, 2 addition products. That is, the reagent acts upon the carbonyl group, giving



Ketones follow the same rule if one of the groups attached to the carbonyl is the methyl radical. Other ketones with conjugate double bonds yield 1, 4 addition products. Thus, from

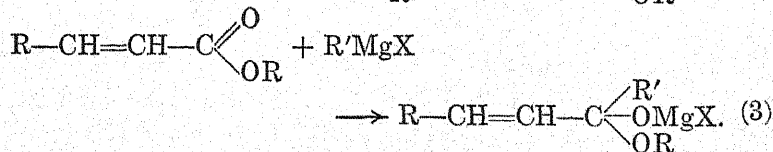
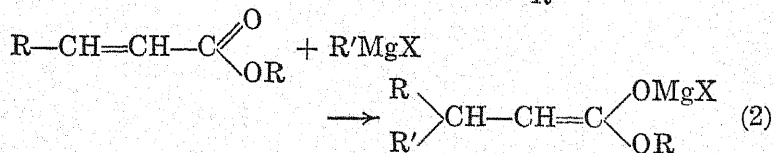
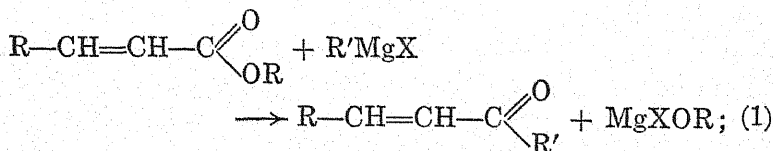


we obtain



On hydrolysis this yields a saturated ketone.

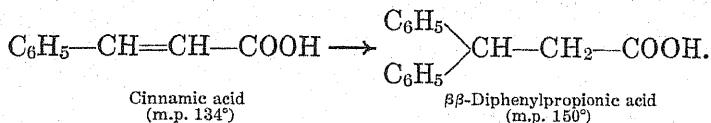
With  $\alpha$ - $\beta$ -unsaturated esters there are three possibilities. The alkoxyl group may be replaced by the radical of the Grignard reagent, or 1, 4 or 1, 2 addition may occur:



\* Kohler and Heritage, *Am. Chem. J.*, **33**, 21 (1905). Kohler and Reimer, *Am. Chem. J.*, **33**, 333 (1905). Kohler, *Am. Chem. J.*, **34**, 132 (1905); *ibid.*, **37**, 369 (1907).

Reactions (1) and (3) give rise to the same products, and we cannot determine which mechanism represents the actual process. If the radical in the Grignard reagent is aromatic, the reaction goes chiefly according to (1) or (3). If the radical is aliphatic, reaction (2) is favored.

Cinnamic acid is converted into  $\beta\beta$ -diphenylpropionic acid by treatment with phenyl magnesium bromide:



The first step in this conversion is probably 1,4 addition. This is followed by a molecular rearrangement.

### ZINC ALKYL REACTIONS

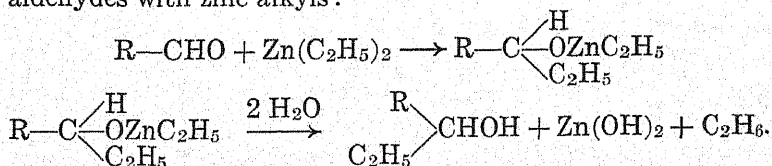
As early as 1852 Frankland\* had reported the preparation of zinc alkyl compounds and had called attention to their remarkable activity. Every year from the time of Frankland's discovery to the beginning of the twentieth century, efforts were made to use the metallic alkides in synthetic work. These attempts were not entirely successful on account of the difficulties encountered in the preparation and use of the reagents.

When ethyl iodide and zinc are heated together in the absence of air, compounds corresponding to the formulas  $\text{C}_2\text{H}_5\text{ZnI}$  and  $(\text{C}_2\text{H}_5)_2\text{Zn}$  are produced. The former is a colorless solid. The latter — zinc ethyl — is a colorless liquid. It boils at 118° and burns spontaneously in an atmosphere of oxygen or air. Other alkyl halides react with zinc in the same way.

Zinc alkyls are hydrolyzed by cold water. The products are zinc hydroxide and saturated hydrocarbons:

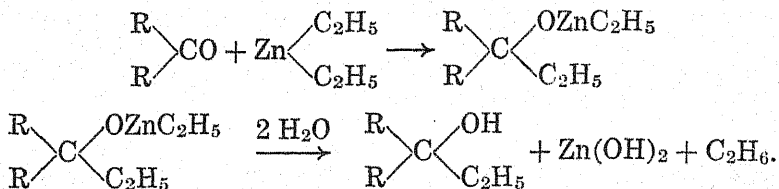


Secondary alcohols are formed through the condensation of aldehydes with zinc alkyls:

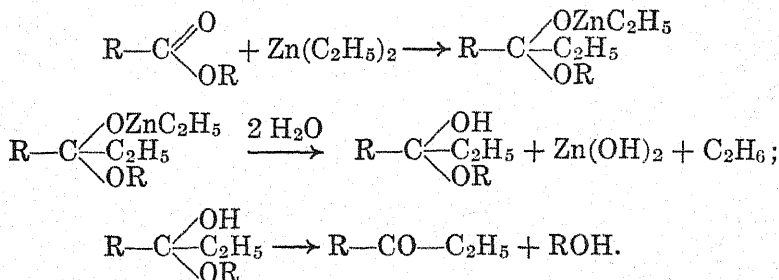


\* Frankland, *Phil. Trans.*, 142, 417 (1852); *Ann.*, 85, 329 (1853).

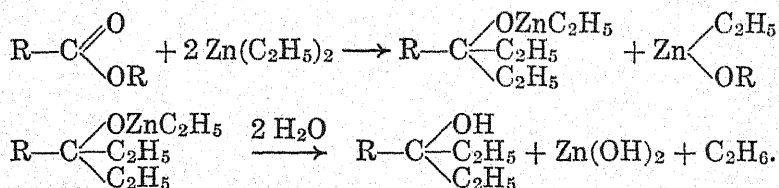
Ketones react with zinc alkyls, forming tertiary alcohols



When an ester is treated with one equivalent of zinc alkyl, a ketone is produced :



With an excess of the zinc alkyl, an ester can be converted into a tertiary alcohol :



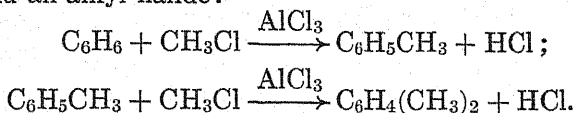
### THE FRIEDEL AND CRAFTS REACTION

The catalytic influence of anhydrous aluminum chloride in effecting condensations between aliphatic halogen compounds and derivatives of benzene, naphthalene, and anthracene was observed by Friedel and Crafts\* in 1876. Applications of the reaction have been extended to almost every type of change which involves the elimination of hydrogen chloride, hydrogen bromide, or hydrogen iodide. The catalytic action of aluminum chloride is an important aid also in many reactions that do not involve the removal of a hydrogen halide.

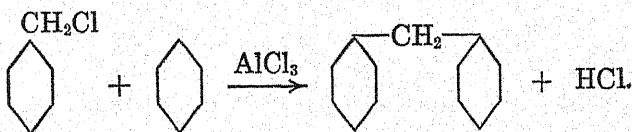
\* Friedel and Crafts, *Ber.*, 10, 1180 (1877); *Compt. rend.*, 84, 1392 (1877).

Ferric chloride, ferric bromide, and the corresponding salts of antimony, zinc, and tin may be substituted for the aluminum salt; but as a rule aluminum chloride is superior to these, and in many cases it is the only reagent of practical value in bringing about the condensations.

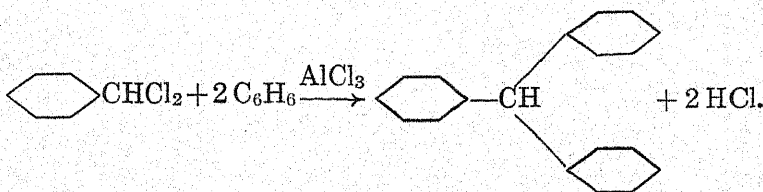
1. **Side chains introduced.** Homologues of benzene may be made by the action of aluminum chloride on a mixture of benzene and an alkyl halide:



The reaction does not stop when one alkyl group has been introduced into the ring. Products containing two or three side chains may be formed at the same time. Separation of the products is accomplished by fractional distillation or crystallization. The halogen atom involved in the reaction must be attached to an aliphatic carbon atom. Chlorobenzene, for example, will not react with an aliphatic hydrocarbon to form a homologue of benzene. Benzyl chloride or any aromatic compound having chlorine or bromine in an aliphatic side chain will respond to this treatment; thus benzyl chloride and benzene yield diphenylmethane:



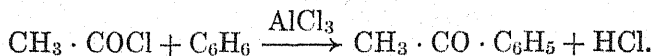
Benzal chloride and benzene yield triphenylmethane:



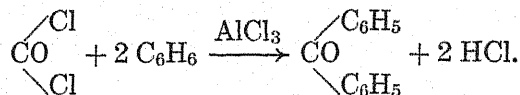
2. **Side chains removed.** A solution of xylene in benzene, when boiled with dry aluminum chloride, is partly converted into toluene. The reaction is reversible, toluene being partly converted into a mixture of xylene and benzene:



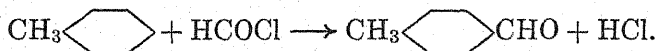
3. Formation of ketones. Acid chlorides (aliphatic or aromatic) react with aromatic hydrocarbons to yield ketones:



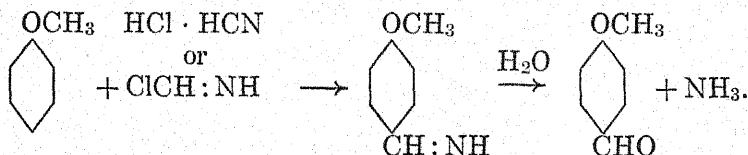
Phosgene reacts in the same way:



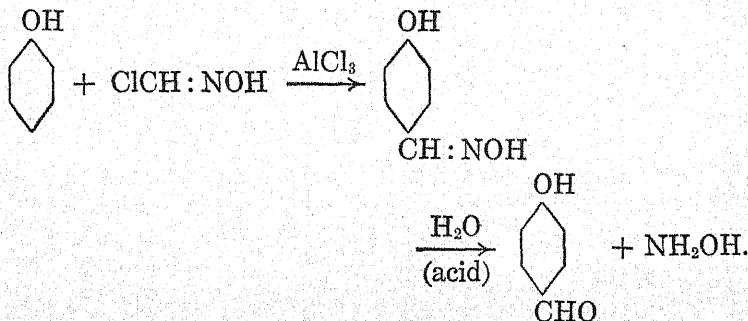
4. Preparation of aldehydes. A mixture of carbon monoxide and hydrogen chloride acts as if it were formyl chloride and, like any acid chloride, condenses with an aromatic hydrocarbon:



A very successful method for introducing an aldehyde group into a phenol, or a phenol ether, consists in treating the compound with a mixture of hydrogen chloride and hydrogen cyanide gases in the presence of aluminum chloride. The condensation product is hydrolyzed by acidifying and distilling with steam:

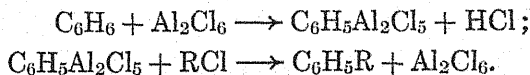


The oxime of chloroformic aldehyde serves also to introduce an aldehyde group:



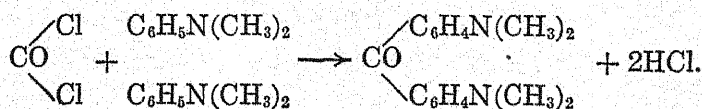


The mechanism of the Friedel and Crafts reaction is not thoroughly understood. An intermediate product may be formed by the action of aluminum chloride on the hydrocarbon, and this, in turn, may act upon the halogen compound:

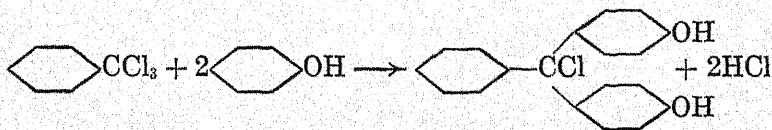


The objection to this theory is that a large quantity of the salt is required, the yield, in most cases, being roughly proportional to the amount of aluminum chloride used. This would not be true if the salt, in the rôle of a true catalyst, could be used repeatedly. Gustavson found that aluminum chloride forms fairly stable compounds with hydrocarbons. He isolated products having the formulas  $\text{Al}_2\text{Cl}_6 \cdot \text{C}_6\text{H}_6$  and  $\text{Al}_2\text{Cl}_6 \cdot 6 \text{C}_6\text{H}_6$ . In the same way many of the condensation products formed by the Friedel and Crafts reaction combine with aluminum chloride. Combination of the salt with the solvent or with a product of the reaction would result in its rapid removal from the field of action, and this may account for the necessity of using large quantities. On this basis, Steele\* supports the claim that aluminum chloride is a true catalyst, and he maintains that it differs from other catalysts only on account of its tendency to become inactive through the formation of stable compounds of the types mentioned.

It is not always necessary to supply a catalyst to secure condensation through elimination of hydrogen chloride. The reaction proceeds spontaneously in many cases. Michler's ketone is prepared by the direct action of phosgene on dimethylaniline:

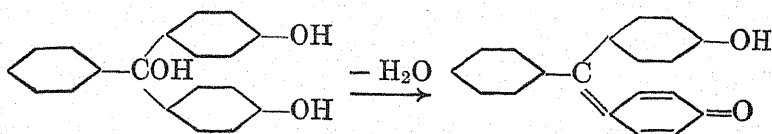


Phenol condenses in the same way with benzotrichloride:



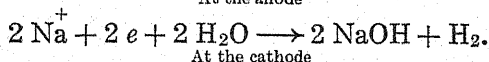
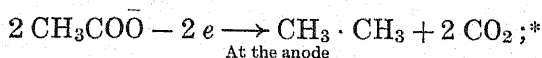
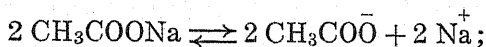
\* Steele, *J. Chem. Soc.*, 83, 1470 (1908).

This chloride is hydrolyzed by water, and the resulting carbinol passes spontaneously into the dye, aurine:

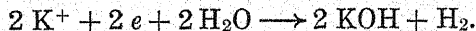
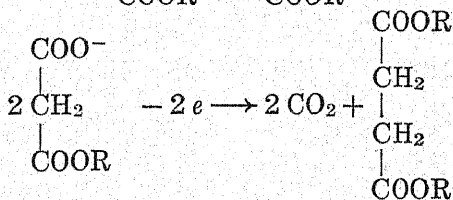
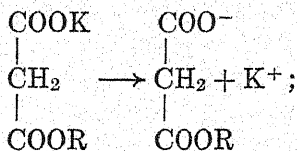


## ELECTROLYSIS OF SALTS

The electrolysis of the salts of organic acids affords a suitable method for making a variety of condensation products. The metal is removed at the cathode, and carbon dioxide is evolved at the anode. Sodium acetate yields ethane:



If malonic acid is half neutralized with potassium hydroxide and half esterified, and then electrolyzed, the chief products formed are succinic ester and carbon dioxide:



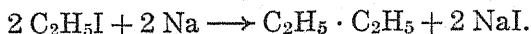
The formation of a ketone by distilling a salt of a carboxylic acid is another type of condensation through loss of carbon dioxide (see pages 68 and 245).

\* The symbol  $e$  is used to represent a unit negative charge, that is, one electron. Each negative ion delivers an electron to the anode, then breaks up into  $\text{CO}_2$  and  $\text{CH}_3$ . Each sodium ion receives an electron from the cathode. It thus becomes an ordinary neutral sodium atom. It immediately decomposes water, liberating hydrogen.



## THE WURTZ SYNTHESIS

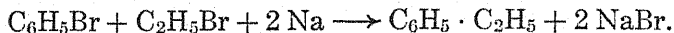
Metallic sodium or sodium amalgam may be used to remove halogens and effect condensation of the resulting radicals. Wurtz used the reaction to build up the homologues of methane:



Fittig applied the same method to the synthesis of aromatic hydrocarbons:

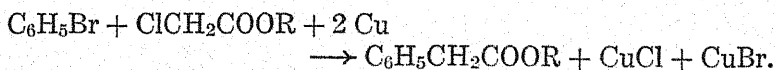


Aliphatic side chains may be introduced into aromatic nuclei by using a mixture of aromatic and aliphatic halides:

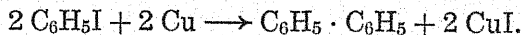


Mixed products are formed, however, when two or more halides are present, for there are equal opportunities for the formation of at least three different compounds. In the example given above ethylbenzene, biphenyl, and butane would be formed.

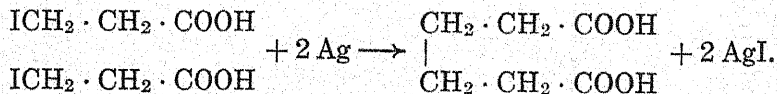
Other metals may be used as condensing agents. Finely divided copper (molecular copper), prepared from copper sulfate by reduction with zinc,\* removes the halogen atoms from chloroacetic ester and bromobenzene, forming phenylacetic ester; the temperature required is 180° to 200°:



At 230° copper removes iodine from phenyl iodide, forming biphenyl:



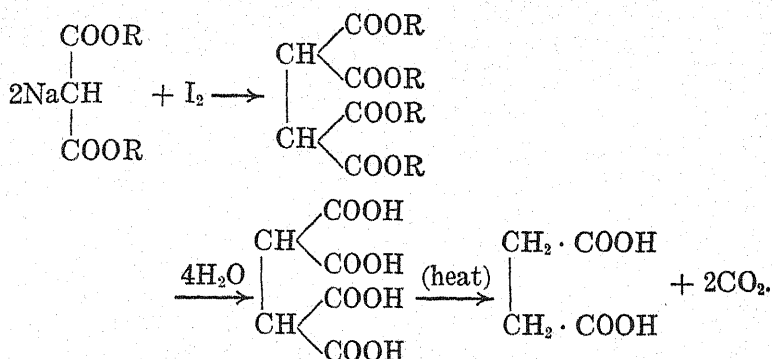
Molecular silver† was used by Gomberg and his coworkers in the preparation of triarylmethyls (p. 266), and silver powder was used by Wislicenus in the preparation of adipic acid from  $\beta$ -iodopropionic acid:



\* Gattermann, *Ber.*, 23, 1219 (1890).

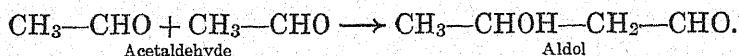
† Gomberg and Cone, *Ber.*, 39, 3274 (1906).

The use of a halogen to remove a metal is equally successful. Iodine acts upon sodioacetoacetic ester, forming diethyldiacetyl succinate (p. 426), and sodiomalonic ester responds in the same way, yielding ethane tetracarboxylic ester, a stable crystalline compound, which on hydrolysis decomposes into carbon dioxide and succinic acid :

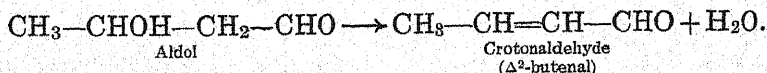


### THE ALDOL CONDENSATION

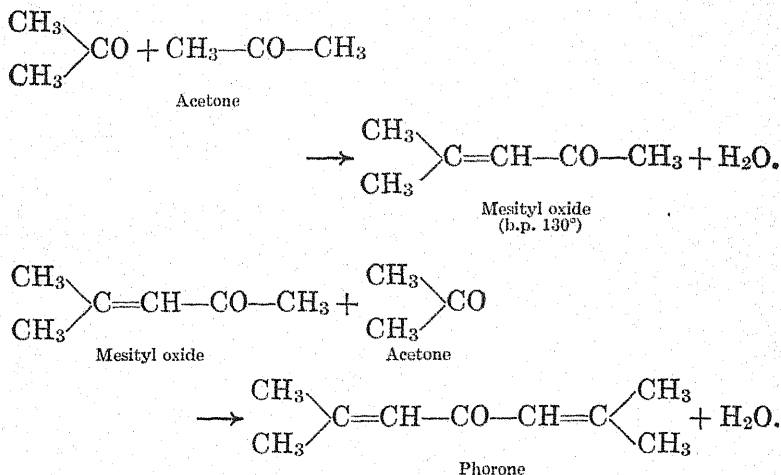
The aldol condensation is a reaction of aldehydes and ketones in which a bond is established between the  $\alpha$ -carbon atom of one molecule and the carbonyl group of another. It is exemplified by the behavior of acetaldehyde in solution with potassium carbonate or sodium ethylate :



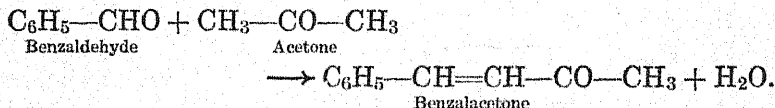
The reagents that induce this change are alkali carbonates, sodium or potassium ethylate, dilute solutions of inorganic hydroxides, hydrochloric acid, and, in some cases, zinc chloride, sulfuric acid, or acetic anhydride. In many cases zinc chloride and the acids carry the reaction beyond the aldol stage by the removal of a molecule of water. The reaction is then referred to as the crotonaldehyde condensation.



Acetone, saturated with hydrogen chloride and allowed to stand for some time, yields mesityl oxide and phorone :



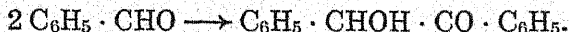
Benzaldehyde and acetone combine when boiled with a 10 per cent aqueous solution of sodium hydroxide.\* In this case the aldol condensation is followed by dehydration even in the presence of dilute alkali:



When *o*-nitrobenzaldehyde is used in this reaction, the aldol can be isolated. It is easily converted into the unsaturated compound by treatment with hot acetic anhydride.†

### THE BENZOIN CONDENSATION

When an alcoholic solution of benzaldehyde is warmed with a small quantity of potassium cyanide, it is converted almost quantitatively into benzoïn:



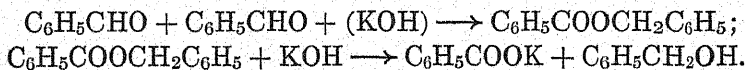
The action of the cyanide ion is specific. No other catalyst for this reaction has been found. The benzoïn condensation is accomplished in alkaline solution only. Free hydrocyanic acid does not furnish a sufficient concentration of cyanide ions. The reaction differs fundamentally from the aldol condensation,

\* Claisen, *Ber.*, 14, 2471 (1881). † Baeyer and Drewsen, *Ber.*, 15, 2857 (1882).

for it is a reaction between aldehyde groups exclusively. In the aldol condensation hydrogen migrates from the  $\alpha$ -carbon atom of one molecule to the aldehyde group of another. In aromatic aldehydes, and in tertiary aliphatic aldehydes, no hydrogen is present on the  $\alpha$ -carbon atom, and the aldol type of condensation cannot occur.

### THE CANNIZZARO REACTION

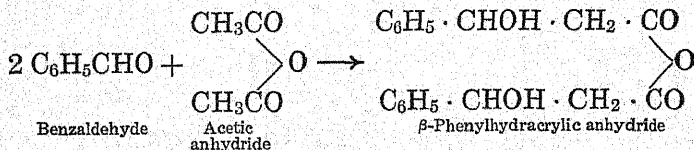
In the absence of cyanide ions aromatic aldehydes and tertiary aliphatic aldehydes undergo the Cannizzaro reaction when shaken with a concentrated solution of sodium hydroxide or potassium hydroxide. The reaction consists of an oxidation of half of the aldehyde molecules to the corresponding acid and simultaneous reduction of the other half to the alcohol stage. An ester is formed as an intermediate product. The mechanism by which the ester is formed is not definitely known. It appears as a condensation product of aldehyde molecules in alkaline solution, but its hydrolysis products, the free acid and alcohol, regenerate the ester only in acid solution. The Cannizzaro reaction may be represented as follows:



All aldehydes are susceptible to the benzoin condensation and the Cannizzaro reaction, but the aldol condensation is a faster reaction than either of these, and therefore an aldol is formed when an aldehyde having hydrogen attached to an  $\alpha$ -carbon atom is treated with an alkali.

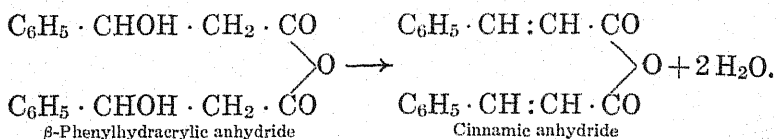
### THE PERKIN REACTION

Perkin prepared cinnamic acid by heating a mixture of benzaldehyde, acetic anhydride, and sodium acetate.\* The reaction may be interpreted as a direct condensation between the acid anhydride and the aromatic aldehyde:



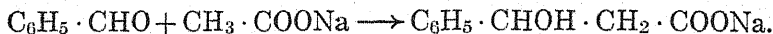
\* William H. Perkin, *Trans. Chem. Soc.*, 31, 389 (1877).

Through the loss of water the condensation product yields cinnamic anhydride:

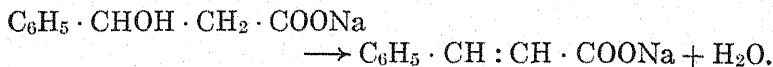


On hydrolysis the cinnamic anhydride yields cinnamic acid,  $\text{C}_6\text{H}_5 \cdot \text{CH} : \text{CH} \cdot \text{COOH}$ .

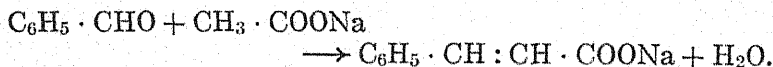
Fittig\* presented a different mechanism, based upon the assumption that it is the sodium salt and not the anhydride of the acid which combines with the aldehyde:



Acetic anhydride was regarded as a dehydrating agent able to convert the condensation product into a salt of cinnamic acid:

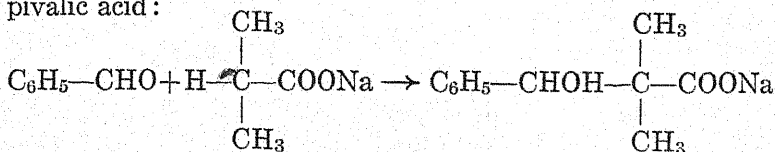


The net result may be indicated by a single equation:



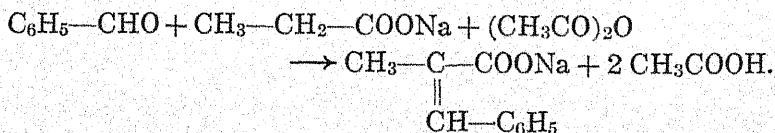
In support of his claim Fittig presented the following evidence:

1. Benzaldehyde condenses with sodium isobutyrate in the presence of acetic anhydride, forming a salt of phenylhydroxypivalic acid:



The reaction stops at this point, for water cannot be eliminated as it is in the case cited above.

2. Benzaldehyde, sodium propionate, and acetic anhydride, when heated to 100°, yield phenylmethacrylic acid:

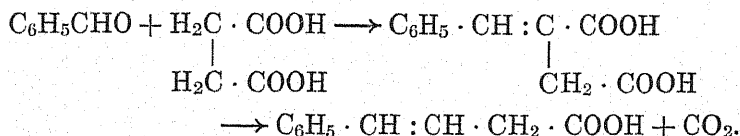


\* Fittig, *Ann.*, 216, 115 (1882).

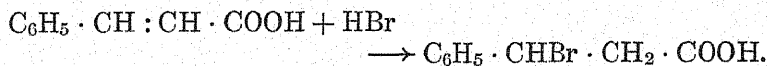
The evidence is not conclusive, however, for cinnamic acid is not formed under any circumstances at 100°, and if the mixture of benzaldehyde, sodium propionate, and acetic anhydride be heated to 180°, cinnamic acid is the principal product. It is obvious that in any system containing a salt of one acid and the anhydride of another, double decompositions may furnish the anhydride or the salt of either acid. There is still some uncertainty concerning the mechanism of Perkin's synthesis.

In the place of benzaldehyde we may substitute its homologues or the halogen, nitro, or hydroxy derivatives of them. Likewise, in place of acetic acid we may use the anhydride and salt of any other fatty acid, or the corresponding derivatives of dibasic acids, or even the aromatic derivatives of the monobasic and dibasic acids.\*

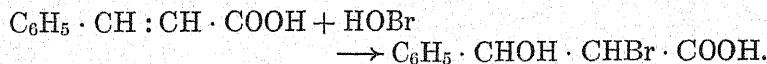
Benzaldehyde, succinic anhydride, and sodium succinate yield a phenyl derivative of vinylacetic acid:



Saturated acids are easily derived from these products. If the double bond is between the  $\alpha$ -carbon atom and the  $\beta$ -carbon atom, as in cinnamic acid, the addition of a halogen acid results in the formation of a  $\beta$ -halogen compound:



With hypobromous acid, an  $\alpha$ -halogen derivative is formed:



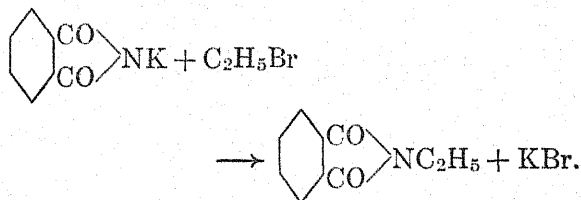
Sodium amalgam, in water or alcohol, introduces two hydrogen atoms; potassium permanganate, two hydroxyl groups; chlorine and bromine form addition products. It is obvious, therefore, that indirectly Perkin's reaction is useful as a means of making saturated as well as unsaturated compounds.

\* For the mechanism of similar reactions see Kohler and Corson, *J. Am. Chem. Soc.*, 45, 1975 (1923). Kohler and Allen, *J. Am. Chem. Soc.*, 45, 1987 (1923).

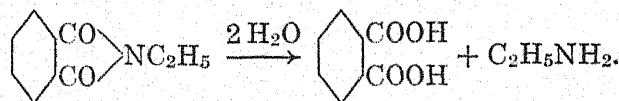
## GABRIEL'S SYNTHESIS

A very useful reaction for the preparation of primary amines has been developed by Gabriel.\* It consists in the treatment of a halogen compound with potassium phthalimide and subsequent hydrolysis of the resulting product.

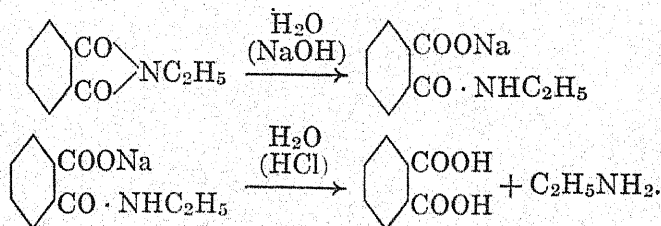
Equimolecular quantities of potassium phthalimide and an alkyl halide are heated in a sealed tube at 150°–200°, from two to five hours:



The reaction mixture is extracted with hot water to remove the potassium bromide and any excess of potassium phthalimide, and the condensation product is then hydrolyzed by boiling it with an acid:



A better yield is obtained by preliminary treatment with sodium hydroxide solution, which half hydrolyzes the compound. Subsequent completion of the process is then accomplished through the agency of hydrochloric acid:



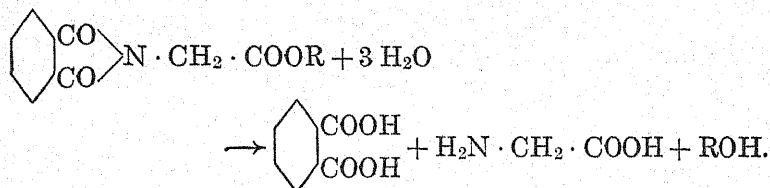
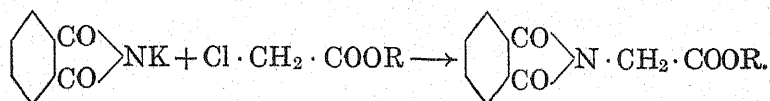
Valuable applications of the reaction were made by Sørensen† and by Fischer‡ in synthesizing amino acids.

\* Gabriel and Hendess, *Ber.*, 20, 2869 (1887). Gabriel, *Ber.*, 47, 3035 (1914); *ibid.*, 51, 1493, 1500 (1918).

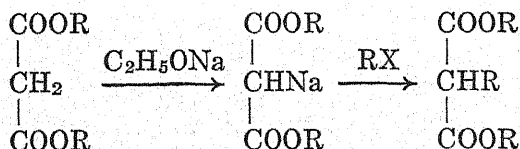
† Sørensen, *Ber.*, 41, 3387 (1908).

‡ Fischer, *Ber.*, 34, 454, 2900 (1901).

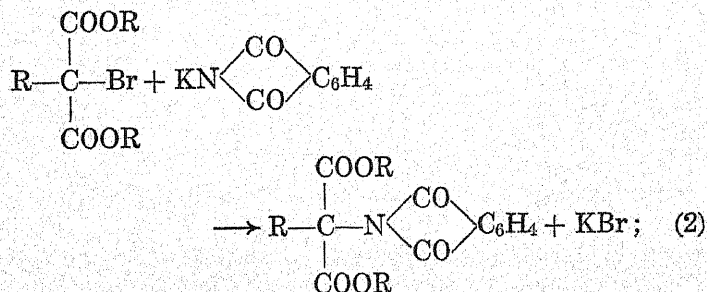
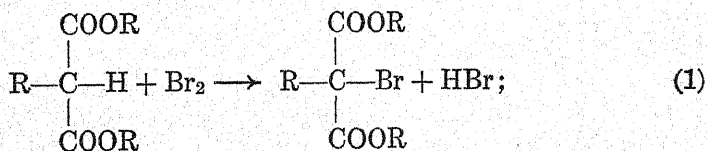
Chloroacetic ester and potassium phthalimide may be used in the preparation of glycine:



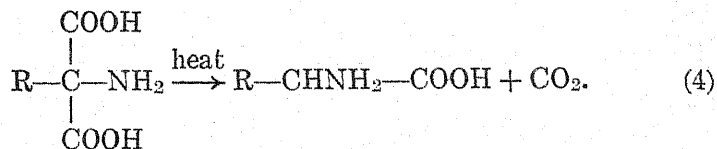
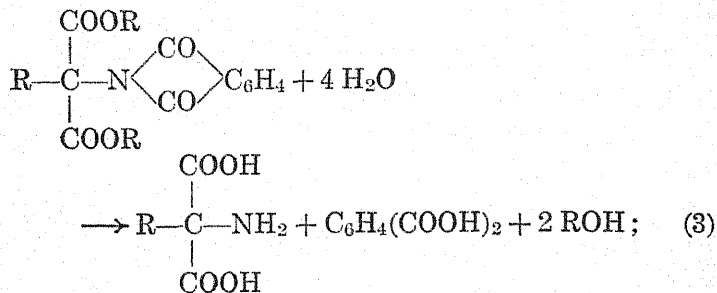
The  $\alpha$ -amino acids may be made from malonic ester by an application of Gabriel's reaction. In order to prepare an acid corresponding to the formula  $\text{R}-\text{CHNH}_2-\text{COOH}$  the radical R is substituted for one of the hydrogen atoms of malonic ester by treating the ester with sodium ethylate and an alkyl halide.



The substituted malonic ester is then converted into the amino acid as indicated below:

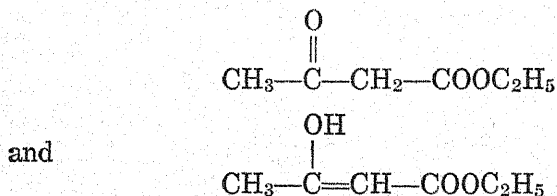






### ACETOACETIC ESTER

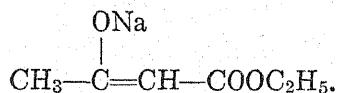
Acetoacetic ester is one of the most useful reagents available for the synthetic processes of organic chemistry. It is, at the same time, an interesting compound from the standpoint of molecular structure. Its configuration was the subject of debate for more than a quarter of a century, and the final solution of the problem established a type of isomerism now called tautomerism. The compound corresponds to two structures:



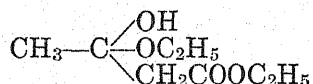
The first, or keto, structure represents the compound as a ketone; the second, known as the enol structure, represents it as an unsaturated alcohol. Acetoacetic ester as ordinarily prepared contains molecules of both types in equilibrium with each other. If a reagent which reacts with the enol form only is added to a solution of the ester, the equilibrium is disturbed as the enol is removed, and the keto form is progressively changed to the enol by an intramolecular rearrangement, one hydrogen atom shifting its position from carbon to oxygen. The entire quantity, therefore, acts as if it were an enol.

On the other hand, if a reagent is used that removes the keto form, the shift occurs in the opposite direction, and the entire sample behaves as if it were a ketone.

The ester is a colorless liquid (b.p. 181°, sp. gr. 1.028), sparingly soluble in water. With ferric chloride it gives a violet-red color due to the presence of a hydroxyl group on a carbon atom which is linked by two bonds to another carbon atom. Metallic sodium reacts with the enol form of acetoacetic ester, liberating hydrogen and forming sodioacetoacetic ester,

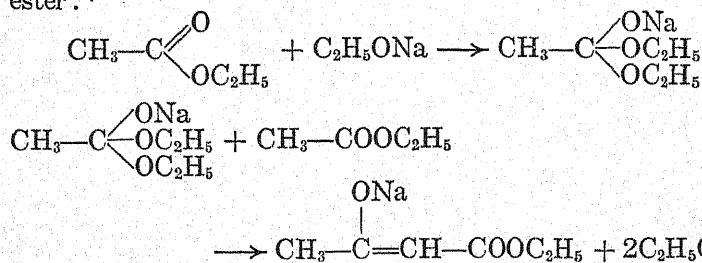


Acetoacetic ester is prepared by the condensation of two molecules of ethyl acetate. The reaction occurs when ethyl acetate is warmed with sodium ethylate (or with metallic sodium and a trace of alcohol). The ethylate ion,  $\text{C}_2\text{H}_5\text{O}^-$ , is a catalyst for this reaction. The formation of an addition product corresponding to the formula



probably represents the first step in the process. The elimination of a molecule of alcohol from this compound would result in the formation of acetoacetic ester.

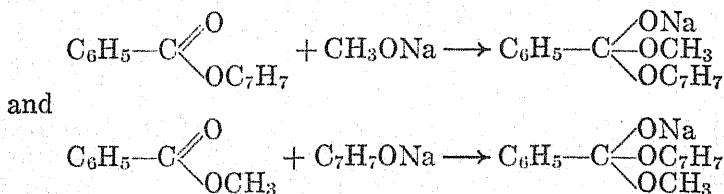
Claisen outlined the reaction under the assumption that an addition product is formed between ethyl acetate and sodium ethylate which, in turn, reacts with another molecule of the ester: \*



That an addition product of the type indicated above is formed was inferred from the fact that benzyl benzoate and sodium methylate form an addition product which can be

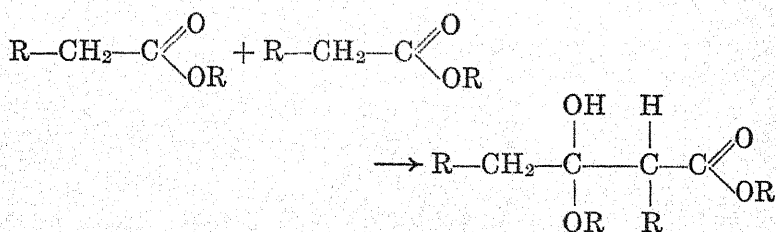
\* Claisen, *Ber.*, 20, 646 (1887).

isolated and which is identical with the product formed from methyl benzoate and sodium benzyolate:

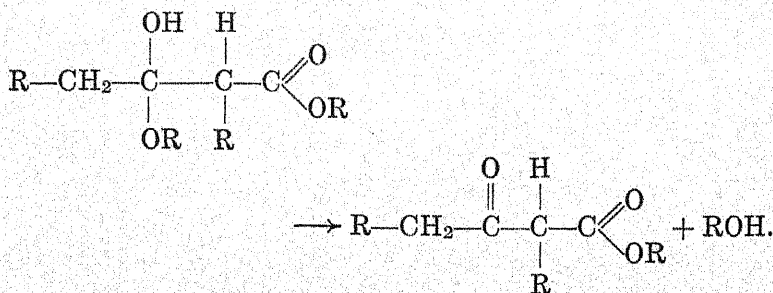


The capacity of ethyl acetate, or of any other ester, to form an addition product with an alcoholate cannot be doubted, but there is no direct proof that such an addition product is an actual intermediate in the formation of acetoacetic ester.

It is generally believed now that the first step in the formation of acetoacetic ester is a condensation of the aldol type occurring between two molecules of ethyl acetate. This is followed immediately by the elimination of a molecule of alcohol. The same mechanism applies to condensations of other esters having hydrogen attached to the  $\alpha$ -carbon atom. Hydrogen migrates from the  $\alpha$ -carbon atom of one molecule to the carbonyl oxygen of another. This migration is accompanied by the establishment of a bond between the  $\alpha$ -carbon atom of one molecule and the carbonyl carbon atom of the other:



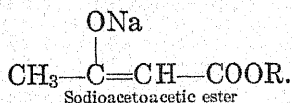
The final step in the process is the elimination of alcohol:



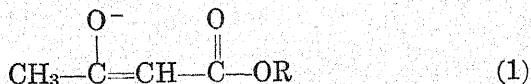
A solution of sodioacetoacetic ester in petroleum ether, cooled to  $-60^{\circ}$  and acidified with anhydrous hydrogen chloride, yields a precipitate of sodium chloride and a solution of the free ester. Evaporation of the solvent at a low temperature leaves the ester in the enol form. It is a liquid that solidifies only when cooled almost to the temperature of liquid air. The keto form crystallizes at  $-39^{\circ}$ , and can be obtained nearly pure by freezing it out of the ordinary mixture.

The relative quantities of the two modifications in any mixture may be determined by a measurement of the refractive index of the mixture. The refractive index is always higher for a compound having a double bond between carbon atoms than for an isomeric body with the double bond between carbon and oxygen. If the indices for the two pure forms are known, the composition of a mixture can be calculated from the observed refraction. The velocity of the approach to equilibrium from either side may be determined by measuring the rate of change in the refractive index or by following the development of color produced by ferric chloride as the quantity of enolic ester increases, or the fading of the color as the keto form increases.

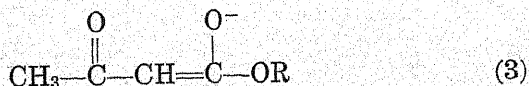
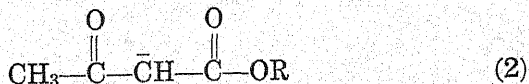
The compound formed when sodium acts upon acetoacetic ester is usually represented by the formula



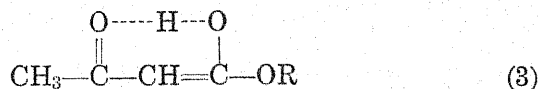
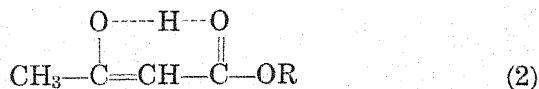
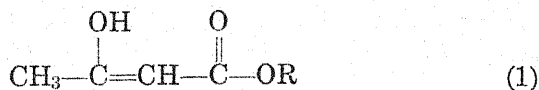
It is a derivative of the enol form of the ester. In alcoholic solution it is extensively ionized, and we shall ordinarily represent the negative ion by the formula



although rapid oscillations of electrons between pairs of adjacent chemical bonds (resonance) would make the following additional forms possible:



Similarly, we may think of the undissociated ester as a resonating molecule corresponding to the following forms:



In formulas (2) and (3) the oxygen atoms are said to be linked to each other by a hydrogen bond, and a cyclic system produced through such bonds is called a *chelate* ring.

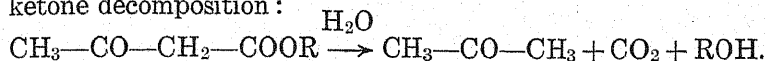
The conversion of the keto to the enol form and vice versa is usually described as a shift in the position of a hydrogen atom between the methylene group and the carbonyl oxygen atom. This implies that the same hydrogen atom is moving back and forth between two possible positions of attachment. The actual mechanism is a more complex process than is represented by this simple picture of the reaction.

These transitions involve the formation of intermediate addition products, and the hydrogen atom does not pass from one position to the other by a direct path. The assumption that an addition reaction is the first step in the process is based upon the fact that the ester may be preserved in either the keto or the enol form if no catalyst is present. A pure sample of either form may be kept for many days in a clean dry quartz vessel. Quartz does not catalyze the change. In a glass vessel equilibrium between the keto and enol forms is soon established. Dust, moisture, an acid, an alkali, or almost any other foreign substance catalyzes the change. The addition product formed with the catalyst must involve forces that do not correspond exactly to normal valence bonds, for such bonds could hardly be established between the ester and such substances as glass and dust particles.

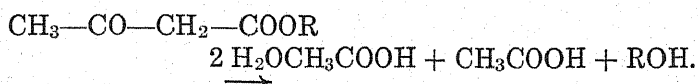
An investigation of the rate of racemization of an optically active derivative of acetoacetic acid and simultaneous measurements of the rate of enolization of the same compound show that enolization cannot consist of a simple reversible change of

keto to enol, but must proceed through some intermediate step.\* The intermediate step in this case is probably an ionization of the compound followed immediately by a change in the electronic configuration of the anion.

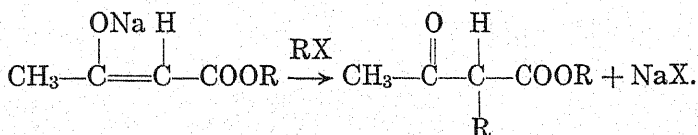
**Hydrolysis of acetoacetic ester.** Acetoacetic ester and its homologues may be hydrolyzed in two ways: (1) When boiled with an acid or a dilute aqueous solution of a base, they undergo the ketone decomposition:



(2) When boiled with a concentrated alcoholic solution of sodium hydroxide or potassium hydroxide, the acid decomposition is effected:

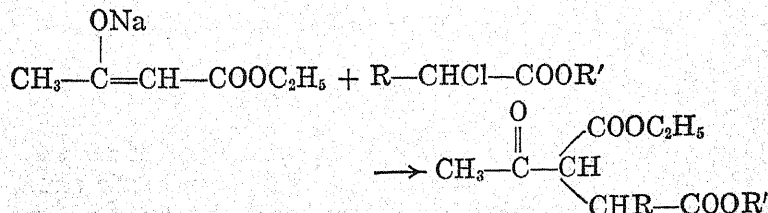


**Acetoacetic ester synthesis.** Alkyl halides act upon sodioacetoacetic ester replacing the metal by an alkyl radical. With rare exceptions, the alkyl radical introduced in this way becomes attached to the  $\alpha$ -carbon atom.

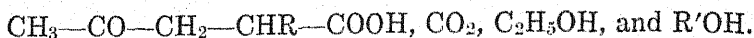


Sodium replaces hydrogen in a monoalkyl-acetoacetic ester, and the metal, in turn, can be replaced by a second alkyl group. By these reactions and subsequent hydrolysis any methyl ketone or any monoalkyl or dialkyl derivative of acetic acid may be prepared.

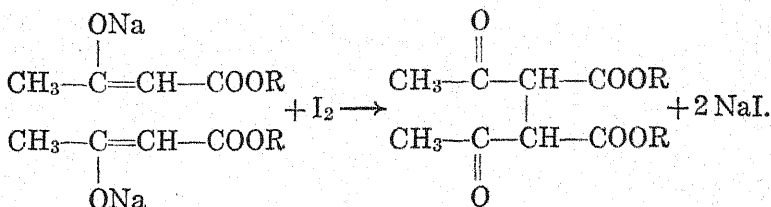
Esters having a halogen atom in the  $\alpha$  position may be used instead of alkyl halides in the reactions outlined above. The ketonic acids are produced in this way:



By the ketone decomposition, this yields



Iodine removes sodium from two molecules of sodioacetoacetic ester, yielding a derivative of succinic acid and sodium iodide:

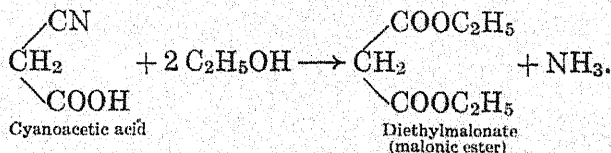


When hydrolyzed by boiling with a solution of potassium carbonate, this compound loses carbon dioxide and yields acetylacetone,  $\text{CH}_3\text{—CO—CH}_2\text{—CH}_2\text{—CO—CH}_3$ .

### MALONIC ESTER

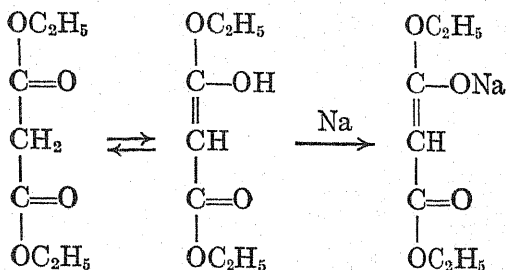
Malonic ester,  $\text{CH}_2(\text{COOC}_2\text{H}_5)_2$ , is a colorless liquid (b.p.  $198.9^\circ$ , sp. gr. 1.061 ( $15^\circ/4^\circ$ ), m.p.  $-49.8^\circ$ ). It has an agreeable odor, dissolves readily in alcohol or ether, and is only slightly soluble in water. A sodium derivative of the ester can be obtained by treatment with metallic sodium or with sodium ethoxide. This derivative is hydrolyzed by water, the free ester being liberated as an insoluble oil.

Malonic ester is prepared from chloroacetic acid through conversion to cyanoacetic acid and subsequent hydrolysis of the cyanide group. The cyanoacetic acid is then boiled with alcohol which is saturated with hydrogen chloride:

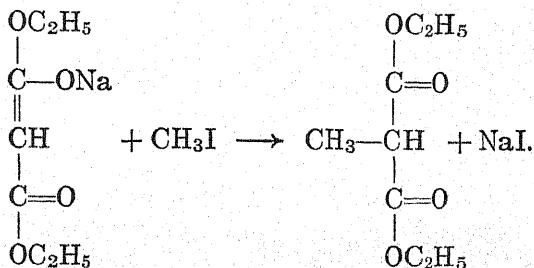


A tautomeric shift, resulting in the formation of an enol structure, is possible here as in the case of acetoacetic ester. A typical malonic ester synthesis is represented in the preparation of propionic acid as follows:

1. Malonic ester is treated with sodium:

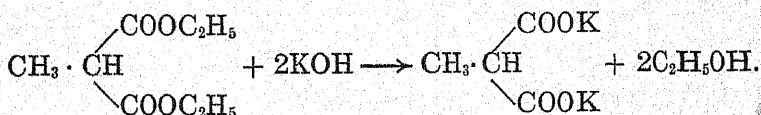


2. The monosodiummalonic ester, dissolved in absolute alcohol, is warmed with methyl iodide:

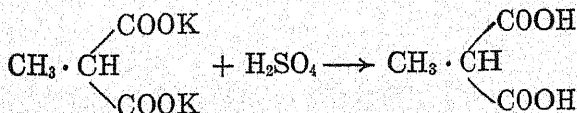


Steps 1 and 2 may be accomplished in one operation by boiling an alcoholic solution of malonic ester with one equivalent of sodium or sodium ethylate and one equivalent of an alkyl halide.

3. The solvent is removed by evaporation, and water is added to dissolve the sodium iodide. The methylated malonic ester is extracted with ether. After evaporating off the ether the product is purified by fractional distillation or by any suitable method, then it is hydrolyzed by boiling it with an alcoholic solution of potassium hydroxide:

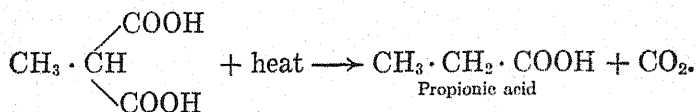


4. Methylmalonic acid is liberated by warming the salt with the calculated quantity of sulfuric acid:



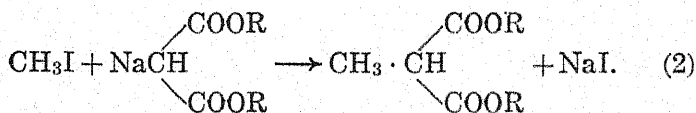
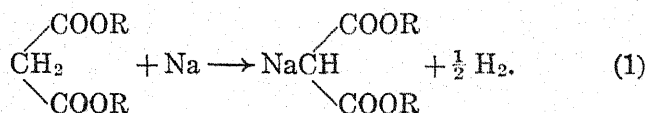


5. One carboxyl group is eliminated by heating the dicarboxylic acid :

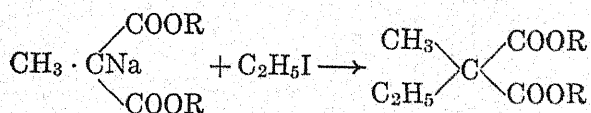
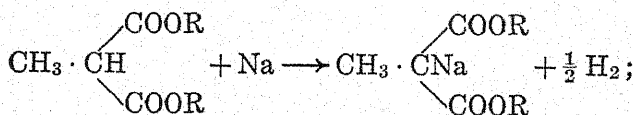


Any compound having two carboxyl groups attached to the same carbon atom may be decomposed by heating it above its melting point. Carbon dioxide is evolved and one carboxyl group is replaced by hydrogen.

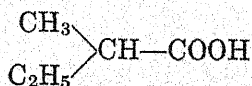
There is no positive evidence that sodiomalonic ester is accurately represented by an enolic structure. The sodium atom may be attached to the central carbon atom and the reaction with an alkyl halide may be a simple double decomposition. The reactions outlined in paragraphs 1 and 2, page 427, are often written as follows :



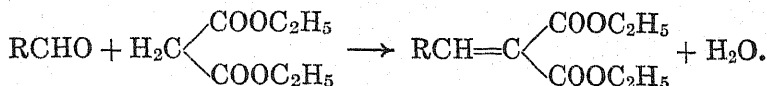
A second alkyl group may be introduced by treating the monoalkyl ester with sodium and an additional alkyl halide.



By hydrolyzing this compound and expelling carbon dioxide, we obtain methylethylacetic acid,

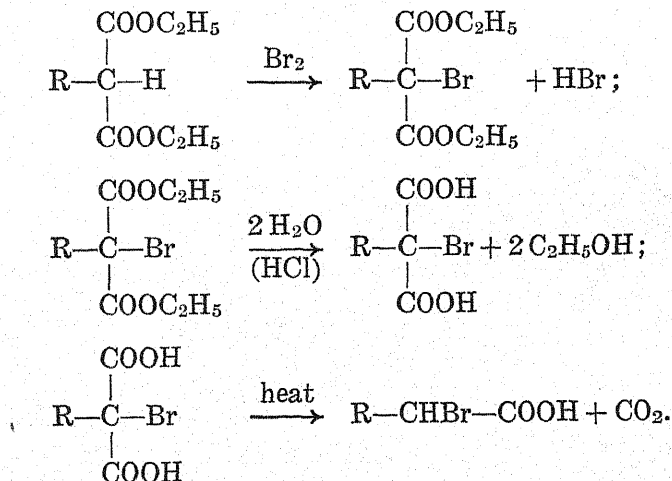


Malonic ester combines with aldehydes and ketones, yielding unsaturated acids:



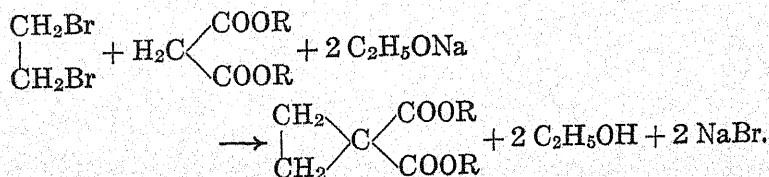
After hydrolyzing this product the resulting dibasic acid is heated to expel carbon dioxide. There remains an unsaturated monobasic acid,  $\text{RCH}=\text{CH}-\text{COOH}$ .

The methylene hydrogen of malonic ester may be replaced by chlorine or bromine as well as by sodium. The  $\alpha$ -halogen acids and  $\alpha$ -amino acids have been synthesized by taking advantage of this fact. The process may be followed by reference to the following outline for the preparation of an  $\alpha$ -halogen acid:



A method for preparing amino acids from malonic ester is explained on page 419.

Ethylene bromide and malonic ester, when heated in alcohol with sodium ethoxide, yield cyclopropane dicarboxylic ester:



The ester may be hydrolyzed to produce the corresponding dibasic acid, and this, in turn, may be converted into a monobasic acid by the application of heat. By a similar process cyclic derivatives of trimethylene bromide and of *o*-xylene dibromide have been made.

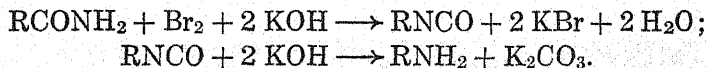
Acetoacetic ester and malonic ester are not the only reagents that may be used in syntheses of the types outlined above. All 1, 3-diketones share, to some extent, the properties of these esters.

## STRUCTURAL REARRANGEMENTS

There are many types of unimolecular reactions which result in the transfer of an atom or a radical from one position to another within the molecule. If such a structural change is rapidly reversible, we refer to the phenomenon as tautomerism. If the reaction is irreversible, we call it a rearrangement. There is no sharp boundary between tautomerism and rearrangement.\*

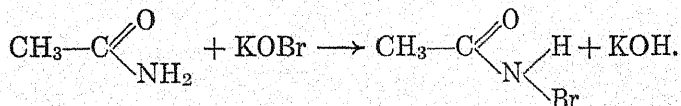
### THE HOFMANN REARRANGEMENT OF ACID AMIDES

An acid amide is converted into an isocyanate by treatment with a warm alkaline solution of bromine.† Since isocyanates are hydrolyzed rapidly by aqueous alkali, this affords a means of converting amides into amines.



In the amide the radical, R, is attached to carbon. In the isocyanate the same radical is attached to nitrogen. Such a shift of a radical from one position to another within a molecule is a typical rearrangement. By using acetamide as an example, the course of the rearrangement may be outlined as follows:

The first step is the formation of a bromoamide.



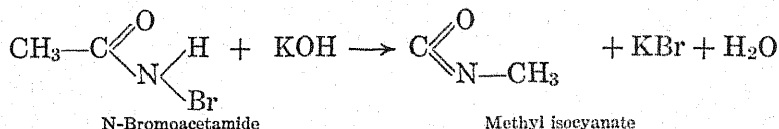
The bromoamide (in this case N-bromoacetamide) is a stable compound and can be isolated. The bromoamide is not ordinarily isolated, for, as a rule, the desired product is an amine and no special care is used to stop the reaction at this stage.

The mechanism of the second step in the process has not been definitely determined. It involves the elimination of HBr

\* For references to the principal papers relating to this class of reactions see Porter's "Molecular Rearrangements." Reinhold Publishing Corporation.

† For experimental details see Porter, Stewart, and Branch's "Methods of Organic Chemistry." Ginn and Company.

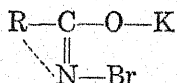
from the nitrogen and a shift of the alkyl radical from carbon to nitrogen. A readjustment of valence bonds occurs and an isocyanate is formed:



Stieglitz advanced the theory that this reaction proceeds through two distinct steps: (1) The elimination of HBr from the bromoamide and formation of an unstable compound of

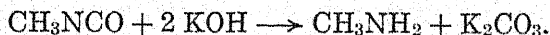
univalent nitrogen having the formula  $\text{CH}_3-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{N} \end{array}$ . (2) The spontaneous rearrangement of this intermediate product. This theory presents a picture of the Hofmann reaction that is easily visualized, but the tendency now is to give up the idea of the existence of an intermediate compound containing univalent nitrogen and to assume that a bond is established between the alkyl radical and the nitrogen atom before the HBr molecule is eliminated or that the establishment of this bond and the elimination of HBr are simultaneous events.

Since an alkali is a necessary reagent, it is presumably a salt of the bromoamide that rearranges. The formula of the intermediate product may be written



As the secondary valence bond between the carbon radical, R, and the nitrogen atom (represented by the dotted line) becomes stronger, the R—C bond becomes weaker; and finally a complete readjustment of valence electrons is accomplished.

The final step in the process of converting an amide into an amine is the hydrolysis of an isocyanate. No rearrangement is involved in this stage of the reaction.



The laboratory procedure for making methylamine follows:

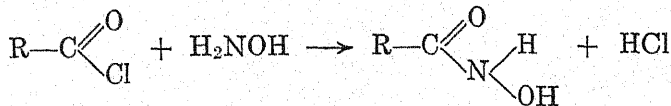
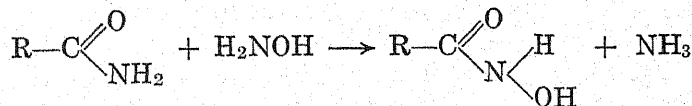
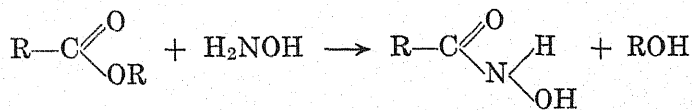
To a mixture of 25 grams of acetamide and 70 grams of bromine a 2 N solution of sodium hydroxide is added until the red color of the mixture changes to a bright yellow. The mixture is then added slowly to 200 cc. of

6 N sodium hydroxide solution and heated to 70° C. until it becomes colorless. The time required for this part of the operation is usually thirty minutes, and during this period the temperature should not go above 75° C. Methylamine is obtained from the solution by distillation with steam. It is collected in 6 N hydrochloric acid. After evaporation to dryness the methylamine hydrochloride is extracted from the solid residue with hot absolute alcohol. Free methylamine is obtained from the hydrochloride by treatment with a base.

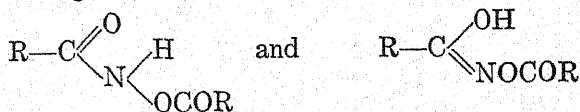
Aromatic acid amides, as well as the aliphatic amides, are susceptible to the Hofmann rearrangement. Important papers relating to the reaction are listed below.\*

### THE LOSSEN REARRANGEMENT

The hydroxamic acids are crystalline solids. They are prepared from esters, acid anhydrides, acid chlorides, or amides in inert solvents by treatment with hydroxylamine.†



When acid chlorides, or acid anhydrides, are used in excess, the products formed are esters which exist in tautomeric forms corresponding to the formulas



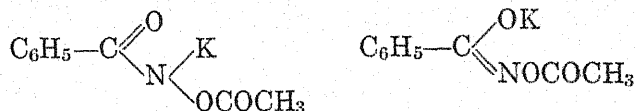
These esters, as well as the free hydroxamic acids, form salts when treated with bases.

\* Hofmann, *Ber.*, 15, 407 (1882). Whitmore, *J. Am. Chem. Soc.*, 54, 3274 (1932). Schroeter, *Ber.*, 42, 2336 (1909). Stieglitz, *Proc. Nat. Acad. Sci.*, 1, 196 (1915). Ingold and Smith, *J. Chem. Soc.*, 1931, 2752.

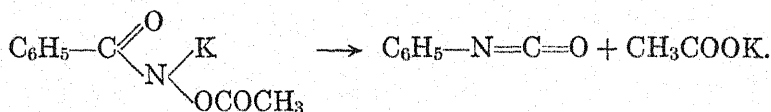
† Lossen, *Ann.*, 252, 170 (1889); *ibid.*, 281, 169 (1894).

Lossen observed that when the acetyl derivative of benzhydroxamic acid is warmed with a base, phenyl isocyanate is produced.

This result can be achieved only through a rearrangement in which the phenyl group becomes detached from a carbon atom and attached to the adjacent nitrogen atom. Using potassium hydroxide as the base in this reaction, we may assume the immediate formation of a salt corresponding to one or both of the following formulas :

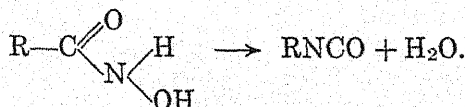


The salt decomposes, yielding phenyl isocyanate and potassium acetate.

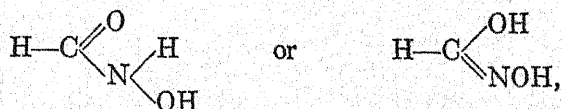


Salts of this type undergo the rearrangement very readily. Some of them, even when dry and in the solid state, decompose with explosive violence; and the products obtained under these conditions prove that the usual migration of an alkyl or aryl radical from carbon to nitrogen has occurred.

The free hydroxamic acids rearrange in the same way when heated alone or with dehydrating agents.



Formhydroxamic acid (m.p. 82°), corresponding to one of the following structures,



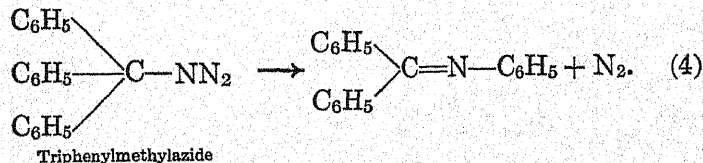
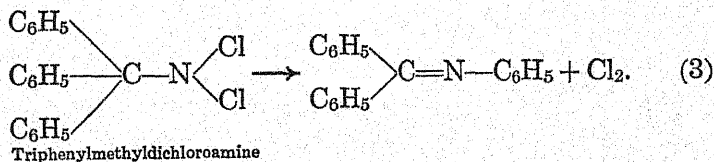
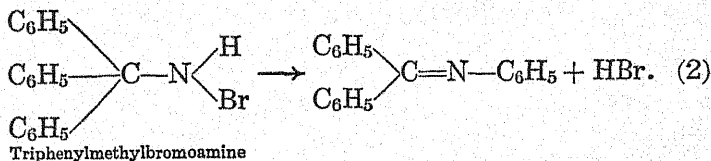
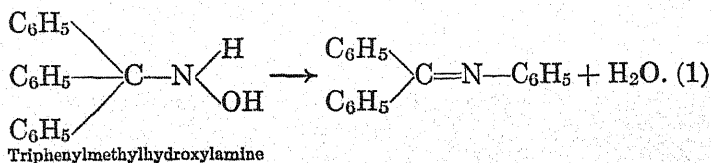
explodes when heated to a temperature above its melting point, yielding carbon monoxide and hydroxylamine; but in aqueous alkaline solution it undergoes the rearrangement, yielding water, carbon dioxide, and ammonia.

## THE STIEGLITZ REARRANGEMENT

In order to test the theory that rearrangement follows the production of a radical containing univalent nitrogen, Stieglitz studied compounds of the following types:

- (1)  $(\text{C}_6\text{H}_5)_3\text{CNHOH}$       (3)  $(\text{C}_6\text{H}_5)_3\text{CNCl}_2$   
 (2)  $(\text{C}_6\text{H}_5)_3\text{CNHBr}$       (4)  $(\text{C}_6\text{H}_5)_3\text{CNN}_2$

The radical  $(\text{C}_6\text{H}_5)_3\text{CN}$  would be formed from (1) by loss of water, from (2) by loss of hydrogen bromide, from (3) by loss of chlorine, and from (4) by loss of nitrogen. In each case it was anticipated that one of the phenyl groups would migrate from carbon to nitrogen, forming benzophenone phenylimide,  $(\text{C}_6\text{H}_5)_2\text{C}=\text{N}-\text{C}_6\text{H}_5$ . This result was achieved in every instance. Water was removed from (1) by a dehydrating agent. Hydrogen bromide was removed from (2) by an alkali. Heat alone caused the rearrangement of (3) and of (4).

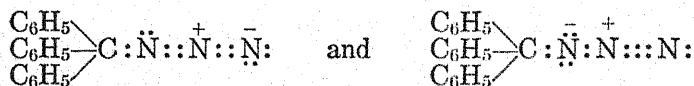


The results in this series of experiments gave strong support to the Stieglitz assumption that a compound containing uni-



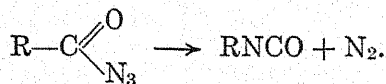
valent nitrogen is an intermediate product in all rearrangements of this type. This theory has not been definitely disproved, but it is no longer regarded as a thoroughly satisfactory representation of the processes involved in the rearrangements of amides, azides, and hydroxamic acids. Some of these reactions have been under investigation for many years. The conditions under which the transformations can be brought about have been determined experimentally, and the molecular structures of the reacting compounds and of the final products have been established with certainty; but the exact mechanisms through which these structural modifications are accomplished remain obscure.

The formula shown above for triphenylmethylazide does not indicate the structure of the molecule. There is evidence (based upon X-ray photographs of crystalline azides) that the three nitrogen atoms are in line. Triphenylmethylazide is a resonating compound. The following electronic distributions represent possible structures:



### THE CURTIUS REARRANGEMENT

The rearrangement of acid azides to isocyanates was discovered by Curtius.\* The reaction is caused by heat alone, and is represented by the equation



The acid azides are prepared from acid chlorides in inert solvents by the action of sodium azide.† If the mixture is

\* Curtius, *J. prakt. Chem.*, (2) 63, 428 (1901). Curtius and Darapsky, *Ber.*, 35, 3229 (1902).

† Sodium azide, a colorless crystalline salt, is made by passing nitrous oxide over sodium amide:



Pure hydrazoic acid,  $\text{HN}_3$ , is unstable. It decomposes into hydrogen and nitrogen. A dilute solution of the acid may be obtained by the action of nitrous acid on hydrazine hydrate:

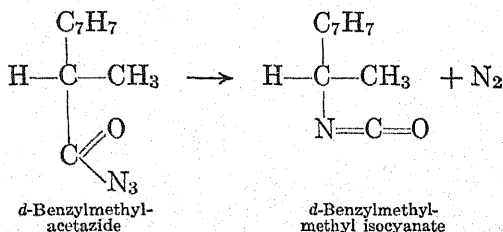


warmed, an isocyanate can be obtained without the necessity of isolating the intermediate acyl azide.\*

Benzazide, when heated alone at 80°, decomposes explosively, but when dissolved in dry benzene or toluene and warmed on a water bath, it yields nitrogen quietly and at a measurable rate.



Jones and Wallis found it possible, through the Curtius rearrangement, to transfer an asymmetric radical from carbon to nitrogen without racemization.† Optically active *d*-benzylmethyl-acetazide was dissolved in benzene and warmed to 35°. Nitrogen escaped and an active isocyanate was obtained.



This remarkable result stands as substantial evidence that the asymmetric carbon atom had become attached to the nitrogen atom before the carbon to carbon bond was broken. It is highly probable that a free asymmetric radical would racemize at once.‡

## THE BECKMANN REARRANGEMENT

Beckmann replaced the hydroxyl group in benzophenone oxime with chlorine through the agency of phosphorus pentachloride, and the chlorine was in turn replaced by hydroxyl through the action of an alcoholic solution of sodium hydroxide.§

\* Methyl isocyanate is made by adding acetyl chloride to a cold amyl ether solution of sodium azide. The solution is then warmed to 60° or 70° until no more nitrogen is evolved. The yield of methyl isocyanate is almost quantitative.

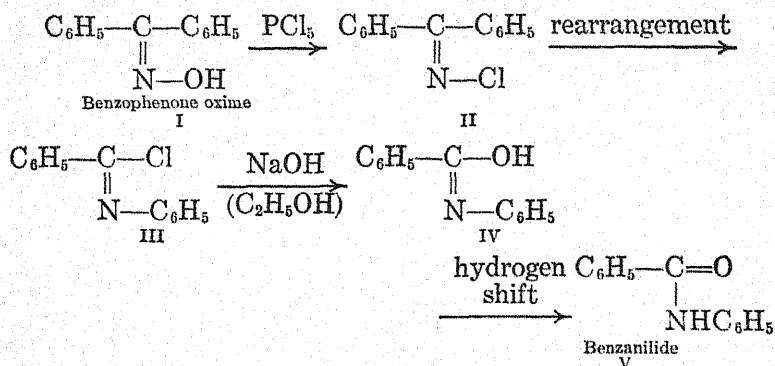
† Jones and Wallis, E. S., *J. Am. Chem. Soc.*, **48**, 169 (1926).

Wallis, E. S., *J. Am. Chem. Soc.*, **51**, 2982 (1929), and *Proc. Nat. Acad. Sci.*, **16**, 215 (1930).

‡ This is a controversial matter. The author is expressing a personal opinion. The Jones and Wallis experiment is interpreted by the majority of chemists as evidence of stability in free radicals. It is assumed that free radicals are stabilized by forming addition products with various solvents or by ionization.

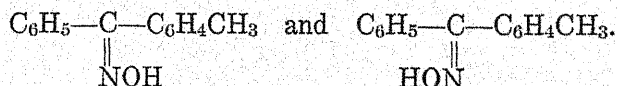
§ Beckmann, *Ber.*, **19**, 988 (1886); *ibid.*, **20**, 2580 (1887); *ibid.*, **27**, 300 (1894).

The resulting product was not the original benzophenone oxime but an isomeric compound — benzanilide — identical with the product obtained by the action of benzoyl chloride on aniline. Beckmann assumed that the alteration in structure was accomplished by an exchange of positions between the atoms or groups attached to carbon and nitrogen, and he outlined the mechanism of the change as follows :

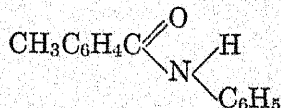


His theory concerning the course of the reaction was not confirmed by experimental evidence, but there remained no doubt about the fact that through the action of the reagents mentioned the compound of formula I was converted into the substance represented by formula V.

Unsymmetrical ketones yield isomeric oximes. Phenyltolylketone, for example, reacts with hydroxylamine, yielding two oximes which are represented by the following formulas :

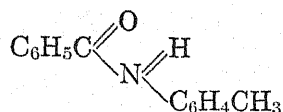


Each of these oximes undergoes the Beckmann rearrangement when treated with phosphorus pentachloride or acetic anhydride and hydrogen chloride. The product obtained from one of the oximes is the anilide of toluic acid,



The formation of this compound is accomplished through a shift of the phenyl group,  $\text{C}_6\text{H}_5$ , from carbon to nitrogen.

The product derived from the other oxime is benzotoluidide,

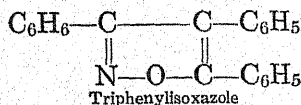


This compound is formed through the migration of the tolyl group,  $\text{C}_6\text{H}_4\text{CH}_3$ , from carbon to nitrogen.

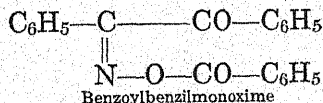
In 1891 Hantzsch reached the conclusion that the exchange of places between the hydroxyl group and a carbon radical in an oxime must occur between groups that are on the same side of the double bond. He recommended the use of the Beckmann rearrangement as a means of determining the structure of the isomeric oximes, assuming in each case that the exchange of positions occurs between groups on the same side of the oxime molecule — a *cis*-interchange.\*

Over a period of more than thirty years this theory was applied and structural formulas were assigned accordingly to all known oximes, the formulas being determined by identifying the rearranged products and assuming *cis*-interchange.

Between 1921 and 1930 Meisenheimer described experiments which proved the possibility of interchange between the hydroxyl group of an oxime and a carbon radical on the opposite side of the molecule — *trans*-interchange.† Meisenheimer prepared triphenylisoxazole, a cyclic compound corresponding to the formula



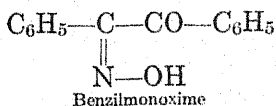
The structure of this compound had been definitely established by synthetic methods. Triphenylisoxazole was oxidized by ozone, and the product was identified as benzoylbenzilmonoxime.



\* A. Hantzsch, *Ber.*, 24, 13 (1891).

† Jakob Meisenheimer, *Ber.*, 54, 3206 (1921). Jakob Meisenheimer and Walter Lamparter, *Ber.*, 57, 276 (1924). Jakob Meisenheimer and Helmut Meis, *Ber.*, 57, 289 (1924).

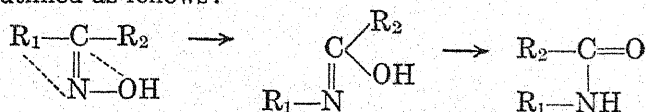
On hydrolysis this yields benzoic acid and a monoxime of benzil.



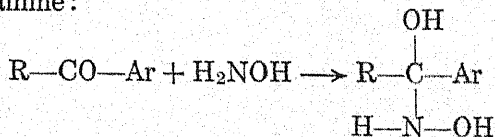
In this oxime of benzil the hydroxyl group and the benzoyl group,  $-\text{CO}-\text{C}_6\text{H}_5$ , must be on the same side of the molecule, for they were members of the original isoxazole ring; yet when this oxime undergoes the Beckmann rearrangement it is the phenyl group, and not the benzoyl group, that becomes attached to the nitrogen atom.

Many investigations have been made in recent years to determine the course of the Beckmann reaction, and nearly every experiment has led to results in harmony with the Meisenheimer theory. On account of the capacity of many oximes to isomerize (that is, the *cis*-form to change to the *trans*-form and vice versa) when brought in contact with certain reagents or when heated, many experimental results cannot be interpreted with certainty.

It seems probable that the first step in the Beckmann rearrangement is the formation of weak bonds (secondary or partial valence bonds) between the atoms involved in the structural change that ultimately occurs. In an environment that supplies the necessary energy these weak bonds become stronger and the original linkages become weaker until an actual change in atomic linkages has been achieved. Representing the newly established bonds by dotted lines, the process may be outlined as follows:

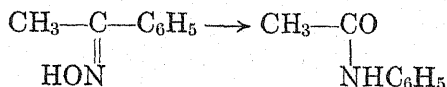


Mixed aliphatic-aromatic ketones do not yield isomeric oximes. To account for this it is assumed that the first step in oxime formation is an addition reaction between the ketone and hydroxylamine:



The radicals R and Ar may then orient the  $\text{H}-\text{N}-\text{OH}$  group in such a way as to insure the elimination of water in

one way only. When such an oxime is subjected to the action of acetic anhydride and hydrogen chloride, it is the aromatic radical that migrates. Acetophenone oxime yields acetanilide:

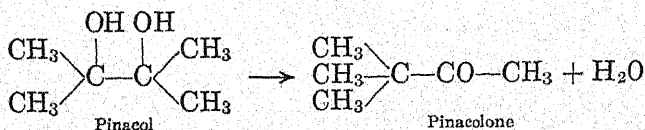


It is not always possible to isolate both forms of an oxime even when the two carbon radicals are aliphatic or when both are aromatic in character.

Many aldoximes exist in two forms, and in assigning structural formulas to these compounds we have depended primarily upon the fact that the acetyl derivative of one member of the pair of geometrical isomers, when warmed with an alkali, readily loses acetic acid, giving rise to a nitrile, whereas the acetyl derivative of the other is hydrolyzed to the original oxime. In assigning structural formulas to aldoximes the assumption has been made that the elimination of water from the oxime can be accomplished only when the hydrogen atom and the hydroxyl group are on the same side of the molecule, and that acetic acid can be removed from the acetyl derivative of an aldoxime only when the hydrogen atom and the acetyl group are on the same side of the molecule. This assumption now appears to be exactly contrary to the truth. It is quite certain that nitriles are formed by a *trans*-elimination of water from an aldoxime and by a *trans*-elimination of acetic acid from the acetyl derivative of an aldoxime.

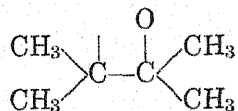
## THE PINACOL REARRANGEMENT

Ditertiary alcohols, known also as pinacols, are obtained from ketones by reduction. Tetramethyl glycol is the principal product obtained when acetone is reduced by mercuric chloride and magnesium in benzene. When this pinacol is heated with sulfuric acid it is converted into an unsymmetrical ketone called pinacolone.\* This reaction is known as the pinacol rearrangement.



\* Pinacol and pinacolone were formerly called pinacone and pinacoline respectively.

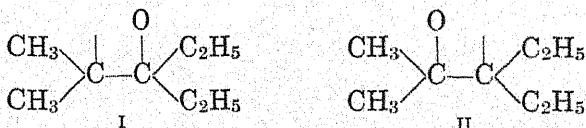
Tiffeneau \* assumes that dehydration is the first step in the process, the intermediate product being an unstable, unsaturated body, represented by the formula



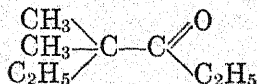
The second step, he maintains, is the migration of a methyl group from the carbon which retains an oxygen atom to the adjacent carbon.

Many other theories relating to the mechanism of this reaction have been advanced. The course of the rearrangement has engaged the attention of chemists for many years, and excellent experimental work has been done in this field. The problem, however, remains unsolved. In the papers listed below the principal theories are elucidated.†

In a symmetrical ditertiary alcohol, such as tetramethyl pinacol, either of the two hydroxyl groups may be eliminated in the formation of water. The groups are similarly placed, and the result is the same if one or the other of the oxygen atoms remains in the molecule. In unsymmetrical pinacols the nature of the rearrangements is not independent of the way in which the water molecule is formed. When, for example,  $\alpha,\alpha$ -dimethyl- $\beta,\beta$ -diethyl-glycol is warmed with sulfuric acid, water may be eliminated in either of two ways as indicated below.



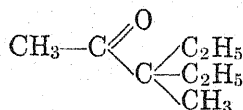
If the elimination occurs as shown in structure I, an ethyl group must migrate with the production of the ketone



\* Tiffeneau, *Ann. chim. et phys.*, 10 (series 8), 322 (1907).

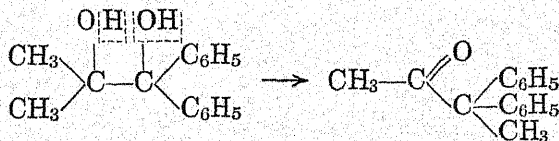
† Montagne, *Rec. trav. chim.*, 24, 105 (1905). Michael, *J. Am. Chem. Soc.*, 42, 787 (1920). Lachman, *J. Am. Chem. Soc.*, 44, 330 (1922). Tiffeneau and Orekhoff, *Bull. soc. chim.*, 33, 195 (1923). Danilow, *Ber.*, 2390 (1927). Bennett and Chapman (bibliography), *Annual Reports Chemical Society* (London), 27, 115 (1930).

If, on the other hand, the intermediate II were formed, a methyl group would shift, forming



When the groups are very much alike (as in this case  $\text{CH}_3$  and  $\text{C}_2\text{H}_5$ ), a mixture of the two possible ketones is produced; but when the groups attached to the two glycol carbon atoms are very different in character, only one ketone is formed. This indicates clearly that the radicals attached to the glycol carbon atoms determine which of the two hydroxyl groups must be removed in the formation of water and which oxygen atom shall remain to become a part of the carbonyl group in the ketone.

Ingold lists three factors that determine the course of a rearrangement of this type: (1) the relative stabilities of the potential anion, (2) the dielectric constant (ionizing power) of the medium, (3) the capacities of the attached radicals to release electrons.\* In the pinacol change the first two factors are of little importance, for (1) the potential anions are identical (hydroxyl groups) and (2) the two isomeric forms would be equally affected by the medium. The determining factor is, therefore, the "electron release capacity" of the carbon radicals attached to the glycol carbon atoms. The groups having the greater tendency to release electrons will cause the hydroxyl group which is attached to the same carbon atom to ionize. In other words, the hydroxyl group which is lost in the pinacol rearrangement is the one attached to the carbon atom which is holding the radical that most readily releases electrons. It is assumed, for example, that the phenyl radical releases electrons more readily than does a methyl radical, and accordingly  $\alpha,\alpha$ -dimethyl- $\beta,\beta$ -diphenyl-glycol should yield, on rearrangement, 3,3-diphenyl-2-butanone.

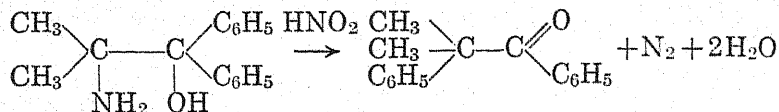


\* C. K. Ingold and C. W. Shoppee, *J. Chem. Soc.*, 1928, 365. C. K. Ingold, *Annual Reports Chem. Soc.*, 25, 134 (1928). J. W. Baker, *Tautomerism*, Rutledge and Sons, 1934.



The experimental result in this case is in agreement with the prediction; but there are exceptions to the rule.

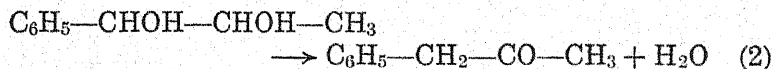
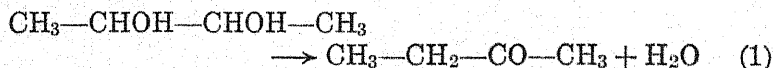
The direction of rearrangement of the  $\alpha$ - $\beta$ -amino-alcohols when treated with nitrous acid seems to be governed entirely by the position of the amino group. In every case the oxygen in the hydroxyl group of the amino-alcohol retains its original position and becomes the carbonyl oxygen of the final product. We have, for example, the following reaction:



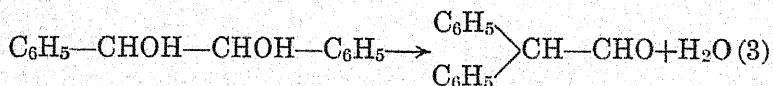
The amino group evidently is not replaced by a hydroxyl group as a preliminary step, for the corresponding pinacol yields a different ketone.

Most of the 1, 2-glycols (dihydric alcohols with the hydroxyl groups on adjacent carbon atoms) are readily converted into aldehydes or ketones, and this conversion involves an intramolecular rearrangement of the pinacol type.

Dissecondary 1, 2-glycols form ketones through the migration of hydrogen and loss of water:



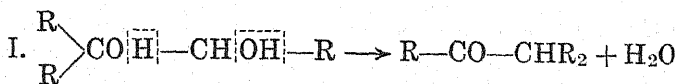
In a few instances an aromatic radical rather than a hydrogen atom makes the shift. Hydrobenzoin is converted into diphenylacetaldehyde in this way:



An analogous result has not been observed in the aliphatic series. An alkyl radical never shifts its position if there is a hydrogen atom attached to the same carbon.

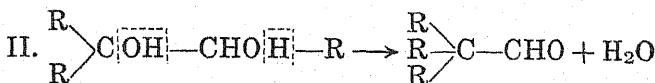
In the case of 1, 2-glycols having one secondary and one tertiary alcoholic hydroxyl group, the rearrangements are classified as semipinacol or semihydrobenzoin types, depending upon the direction in which the carbon radical migrates.\*

\* Tiffeneau and Levy, *Bull. soc. chim.*, 33, 735 (1923).



Semipinacol type

(OH removed from the secondary alcohol group. Radical moves from tertiary to secondary carbon atom, yielding a ketone.)

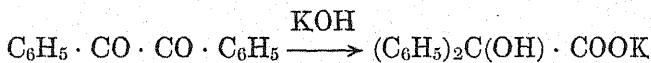


Semihydrobenzoin type

(OH removed from the tertiary alcohol group. Radical moves from secondary to tertiary carbon atom, yielding an aldehyde.)

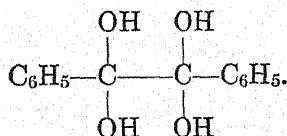
### THE BENZIL REARRANGEMENT AND RELATED CHANGES

Benzil, a yellow crystalline diketone,  $\text{C}_6\text{H}_5 \cdot \text{CO} \cdot \text{CO} \cdot \text{C}_6\text{H}_5$ , which melts at  $95^\circ$  and boils with decomposition at  $347^\circ$ , is converted by hot aqueous alkali into a salt of benzilic acid:

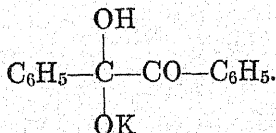


No thoroughly tested and satisfactory explanation of the change has been offered.\*

Tiffeneau assumes the addition of water to each of the carbonyl groups with the formation of



From this point on he applies the mechanism which he developed in connection with the pinacol rearrangement. Scheuing believes the first step is the addition of a molecule of potassium hydroxide to one of the carbonyl groups, yielding the intermediate product

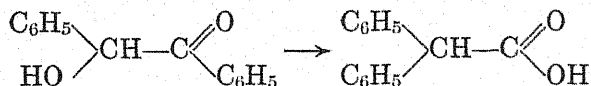


\* Nicolet and Pelc, *J. Am. Chem. Soc.*, **43**, 935 (1921). Michael, *J. Am. Chem. Soc.*, **42**, 787 (1920). Schroter, *Ber.*, **42**, 2336 (1909). Lachman, *J. Am. Chem. Soc.*, **46**, 779 (1924). Tiffeneau, *Rev. gén. sci.*, **18**, 584 (1907).

The second step, he claims, is an exchange of positions between the OK group and a phenyl radical.\*

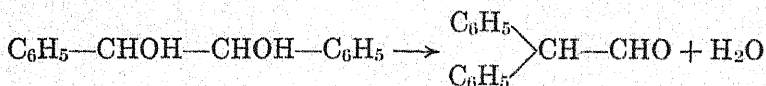
Dissolve 5 g. potassium hydroxide in 10 cc. of water, then add 15 cc. of alcohol. To this solution add 5 g. of benzil and heat the mixture on a water bath for ten minutes. Cool with ice, then filter to obtain the crystalline product, which is potassium benzilate. Dissolve the crystals in 30 cc. of water, heat the solution to the boiling point, and acidify it with hot dilute sulfuric acid. Filter out the precipitated benzilic acid and purify the product by recrystallization from a large volume of hot water (m.p. 150°). The yield is almost quantitative.

Benzoin (m.p. 137°, b.p. 344°) is partly converted into diphenylacetic acid by treatment with 3 M. sulfuric acid at 250°.



Not more than a 10 per cent yield has been obtained; for, at the high temperature required to cause this change, other reactions predominate.

Hydrobenzoin (m.p. 139°) gives a good yield of diphenylacetaldehyde when warmed with sulfuric acid.



It will be observed that benzil adds water in rearranging, benzoin rearranges without loss or gain of water, and hydrobenzoin loses water in the process. In each case one carbon atom is oxidized and an adjacent carbon atom is reduced. In all rearrangements of glycols an intramolecular oxidation and reduction occurs, and a similar generalization can be made with reference to the rearrangements of oximes and of amides.

The structural modification that sometimes occurs when a monohydric tertiary alcohol is dehydrated is known as the Wagner rearrangement.†

When diphenyl-tertiarybutyl-carbinol is warmed with a dehydrating agent it is converted into 3, 3-diphenyl-2-methyl-1-butene.

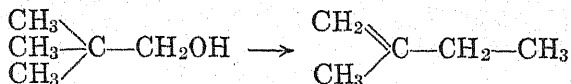
\* Gatterman and Wieland, *Laboratory Methods of Organic Chemistry*. The Macmillan Company, 1932.

† Wagner and Brykner, *Ber.*, 32, 2302 (1899).



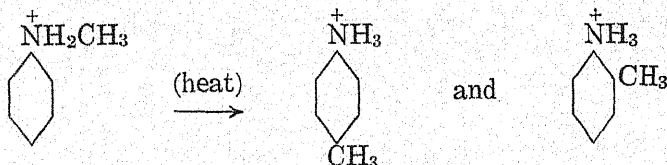
The structure of this unsaturated hydrocarbon was established by Bateman and Marvel.\*

Similarly, tertiarybutyl-carbinol is converted into 2-methyl-1-butene.



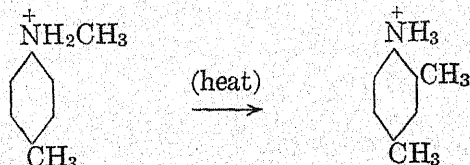
### THE HOFMANN REARRANGEMENT OF SUBSTITUTED AROMATIC AMINES

**Migration of an alkyl radical.** When monomethylaniline is converted into a salt (monomethylaniline hydrochloride) by treatment with hydrochloric acid, then heated to 150°, the methyl group migrates from the nitrogen to the *para* or to the *ortho* position of the ring.† The hydrogen atom occupying the *para* or *ortho* position simultaneously passes to the nitrogen.‡



The rearrangement amounts to an exchange of places between the *para* or the *ortho* hydrogen and the methyl group.

In the same way the hydrochloride of methyltoluidine, when heated, undergoes the Hofmann rearrangement, yielding xylylidine:



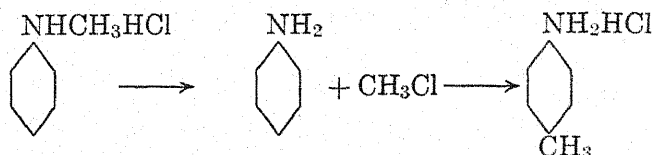
\* Bateman and Marvel, *J. Am. Chem. Soc.*, **49**, 2914 (1927).

† A. W. Hofmann and C. A. Martins, *Ber.*, **4**, 742 (1871).

‡ Mixed products are obtained in rearrangements of this type, but the *para* derivative is predominant. In some cases the *para*-compound is formed almost exclusively.

and from xylidine, by the same procedure, we may obtain mesidine.\*

Many different opinions have been expressed concerning the mechanism of this reaction. A possible course is the following: (1) dissociation of the amine salt with the production of an alkyl halide, (2) a reaction between the alkyl halide and the free amine in which the alkyl group is substituted for hydrogen in the ring and hydrogen halide is regenerated. Michael advanced this theory of the change many years ago.† The conversion of methylaniline into *para*-toluidine, according to this scheme, is accomplished as follows:



Free methylaniline is not changed to toluidine by heat alone, but in the presence of an acid or of metallic salts such as cobalt chloride, cadmium chloride, or manganese chloride the secondary amine undergoes the rearrangement.‡ The presence of the salt insures the formation of an ion of the ammonium type.

If the alkylamine salt dissociates into an alkyl halide as a preliminary step, then any procedure which favors the escape of the amine or of the alkyl halide should reduce the yield of the substitution product. To apply this test Hickinbottom § heated pure ethylaniline with cobalt chloride in a long vertical glass tube. The mixture was heated to 240°–270° for twelve hours. The lower part of the tube was always at a temperature above the boiling point of aniline, and the apparatus was arranged so as to permit the collection of volatile products at any time. The rearrangement proceeded smoothly, but no ethyl chloride was detected and the yield of aniline was negligible.

From the results obtained by Hickinbottom one must conclude that actual dissociation is not a necessary antecedent to the rearrangement. The change in structure may be due to a

\* Porter and Thurber, *J. Am. Chem. Soc.*, 43, 1194 (1921).

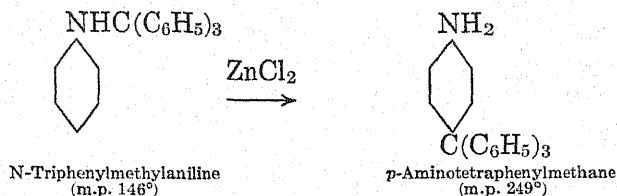
† Michael, *Ber.*, 14, 2107 (1881).

‡ Reilly and Hickinbottom, *J. Chem. Soc.*, 117, 103 (1920).

§ Hickinbottom, *J. Chem. Soc.*, 130, 64 (1927).

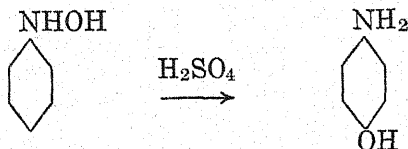
direct reaction between two groups within a single molecule. Other support for this idea will be found in connection with the rearrangement of acetylchloroaminobenzene.

**Migration of a substituted alkyl radical.** N-Triphenylmethylaniline,  $\text{C}_6\text{H}_5\text{NHC}(\text{C}_6\text{H}_5)_3$ , is prepared by mixing a benzene solution of triphenylchloromethane with an alcoholic solution of aniline. At the temperature of a water bath the reaction is completed within fifteen minutes. When heated to  $160^\circ$  with half its weight of zinc chloride it is converted into *para*-aminotetraphenylmethane.\*



The product of the rearrangement is obtained from the fused mass by extraction with alcohol after the zinc chloride has been removed by washing with water.

**Migration of a hydroxyl group.** When heated with sulfuric acid,  $\beta$ -phenylhydroxylamine is converted into *para*-aminophenol.



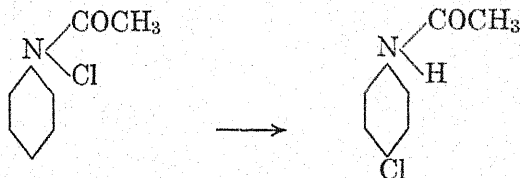
Other arylhydroxylamines behave in the same way if there is an unsubstituted *para* or *ortho* position in the ring.

A commercial process for the reduction of nitrobenzene to *para*-aminophenol depends upon this rearrangement. Nitrobenzene in alcohol is mixed with sulfuric acid and electrolyzed with a lead cathode. Phenylhydroxylamine is formed, and, under these conditions, rearranges immediately. The product, *para*-aminophenol, is used as a photographic developer.

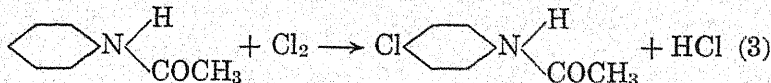
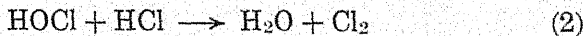
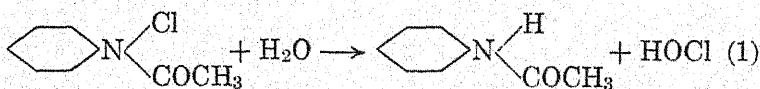
**Migration of an acyl group.** Acetylchloroaminobenzene is made by adding a solution of sodium hypochlorite to a

\* Van Alphen, *Rec. trav. chim.*, 46, 501 (1927).

cold aqueous alkaline solution of acetanilide. The product can be kept for several weeks if dry and protected from light. In pure cold water it is stable in the dark, but if the solution is exposed to light there is a slow conversion of the compound into *para*-chloroacetanilide. In the presence of hydrochloric acid the change is rapid and almost quantitative. The reaction follows the unimolecular law, and the simplest representation of this irreversible change is indicated as follows:



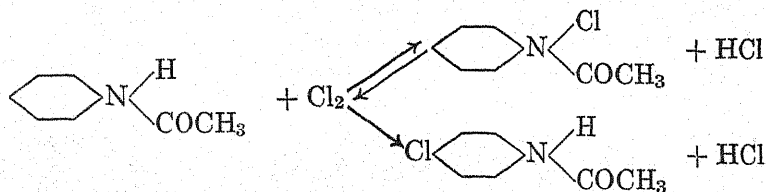
This reaction has been studied systematically in many laboratories, and several theories have been advanced relating to the course of the rearrangement. The mechanism generally accepted at the present time was formulated by Orton and his associates.\* It is assumed that the first step in the process is the hydrolysis of the chloroamine with the production of hypochlorous acid and acetanilide. The hypochlorous acid reacts with hydrochloric acid, to yield chlorine; and finally, as an independent reaction, the acetanilide is chlorinated in the *para* position or in the *ortho* position by the free chlorine.



Chlorine replaces hydrogen on the nitrogen atom as well as in the ring; but the reaction between the amino hydrogen and chlorine is reversible, whereas the reaction between the nuclear

\* Chattaway and Orton, *J. Chem. Soc.*, 75, 1053 (1899). Orton, *Proc. Roy. Soc.*, 71, 156 (1902). Orton and Jones, *J. Chem. Soc.*, 95, 1456 (1909). Orton and King, *J. Chem. Soc.*, 99, 1369 (1911). Kipping, Orton, et al., *Chem. News*, 108, 155 (1913).

hydrogen and chlorine is irreversible. Reaction (3), therefore, is more completely represented as follows:



A different mechanism, supported by much experimental evidence, has been advanced recently. It is assumed that a bond is formed between the chlorine atom and the *para* carbon atom before the chlorine actually severs its connection with the nitrogen atom.\* No means of confirming the idea is, at present, available. The theory is based upon the fact that dry crystals of acetylchloroaminobenzene, when heated or when exposed to ultraviolet light, undergo the rearrangement. No water for hydrolysis is available under these conditions, and no solvent to retain dissociation products is present.†

After a method had been devised for making ordinary elements radioactive a new tool was available for use in the study of reaction mechanisms, and the rearrangement of acetylchloroaminobenzene was investigated once more.‡ Radioactive chlorine was used in the preparation of hydrochloric acid and ordinary chlorine was employed in making acetylchloroaminobenzene. The rearrangement of the ordinary chloroamine (in solution) was then induced by treatment with an equivalent quantity of radioactive hydrochloric acid.

According to the series of equations on page 450 one half of the chlorine which ultimately becomes attached to the ring is derived from the hydrochloric acid and one half comes from the amino group of the chloroamine. With one source of chlorine radioactive and the other inactive, and with methods available for determining the relative amounts of the two kinds of chlorine in the rearranged product, it was thought that the rival mechanisms could be checked. The experiments revealed

\* Porter, *Molecular Rearrangements*, p. 8. Reinhold Publishing Corp., N.Y.

† Porter and Wilbur, *J. Am. Chem. Soc.*, **49**, 2145 (1927). For the action of ultraviolet light upon this compound in various solvents see J. H. Mathews and R. V. Williamson, *J. Am. Chem. Soc.*, **45**, 2574 (1923).

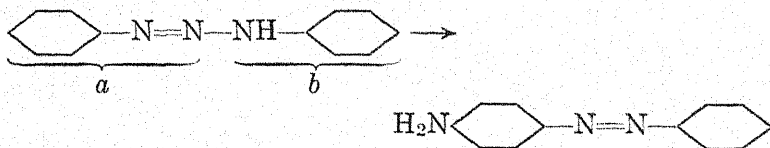
‡ Olson, Porter, Long, and Halford, *J. Am. Chem. Soc.*, **58**, 2467 (1936).



the fact that the final product, *para*-chloroacetanilide, is formed from acetylchloroaminobenzene through two or more paths, but there is no conclusive evidence that the direct shift of chlorine from the nitrogen to the *para* carbon atom is one of the routes followed. It was established that, in aqueous solution, the major part of the product was formed through the course outlined by Orton.

When the rearrangement occurs in the solid phase, or is induced by heating the compound alone to a temperature above its melting point, the Orton mechanism cannot apply. Under such circumstances one of the following assumptions must be made: (1) a direct shift of the chlorine atom from nitrogen to carbon occurs within each separate molecule, or (2) the change is accomplished through a reaction between the amino chlorine of one molecule and the *para* hydrogen atom in another molecule. When the rearrangement occurs in the absence of a solvent we have no means of determining whether it is a unimolecular or a bimolecular reaction.

**Migration of a diazo group.** The conversion of diazoaminobenzene into aminoazobenzene is accomplished by warming an aqueous solution or suspension of the diazoamino-compound with a little aniline hydrochloride:

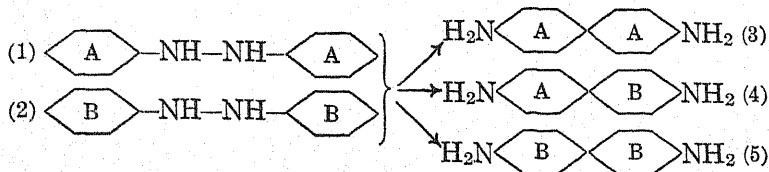


The portion of the molecule marked *a* migrates to the *para* position of the ring in the aniline residue marked *b*.

The benzidine change consists of two rearrangements brought about by warming hydrazobenzene with hydrochloric acid. The first shift gives rise to semidine, and the final readjustment produces benzidine. In each case a group migrates from the nitrogen of an aromatic amine to the *para* carbon atom (see page 214).

In each case, also, the shift is accomplished without an actual dissociation of the molecule into free radicals. Ingold made mixtures of pairs of substituted hydrazobenzenes and induced the rearrangements of these compounds in the presence of each other. If such molecules dissociate in the process of rearrange-

ment, three benzidine derivatives should be formed from each pair of hydrazobenzene derivatives in the mixture, as indicated below :

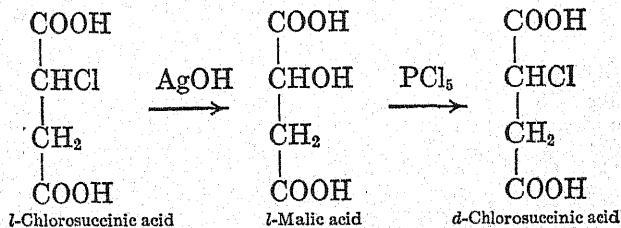


Actually, no compound of type (4) was formed.\* There was no exchange of groups between the compounds (1) and (2).

### THE WALDEN INVERSION

An optically active compound is usually racemized by heat alone or by boiling with an acid or alkali. From the racemic mixture the dextro and lævo forms may be isolated by the methods outlined under *optical isomerism*.

In 1895 Walden prepared *d*-chlorosuccinic acid from *l*-chlorosuccinic acid without complete racemization. The change was accomplished by replacing the chlorine atom by a hydroxyl group through the agency of silver hydroxide, then replacing the hydroxyl group by chlorine through the action of phosphorus pentachloride:

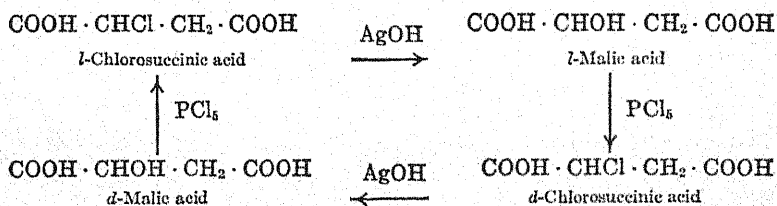


Somewhere in the process outlined by these formulas a change in structure occurs. Either the hydroxyl group fails to take the position previously occupied by chlorine, or the phosphorus pentachloride fails to introduce chlorine in the position occu-

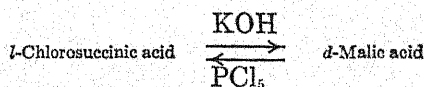
\* Ingold and Kidd, *J. Chem. Soc.*, 1933, 984. A mechanism based upon the formation of a cyclic intermediate product has been outlined by Sielisch and Grund. Sielisch and Grund, *Über den Mechanismus intra- und intermolekularer Reaktionen*, Berlin, 1932.

pied by the replaced hydroxyl. The fact that the sign of the optical rotation changes as a result of the second reaction does not imply that the change in positions of the groups around the asymmetric carbon atom occurs also in this step, for there is no reason to assume that hydroxy and chlorine compounds of like structure should have similar optical properties. But when the hydroxyl group is replaced by chlorine, regenerating chlorosuccinic acid, one would expect to find either racemization or a restoration of the original optical properties. The product actually obtained is the mirror image of the original substance, and therefore, somewhere along the line, an inversion occurs.

Silver hydroxide acts upon *d*-chlorosuccinic acid, converting it into *d*-malic acid, which in turn yields *l*-chlorosuccinic acid. We have, therefore, a complete cycle:



If potassium hydroxide be substituted for silver hydroxide, a different malic acid is produced:

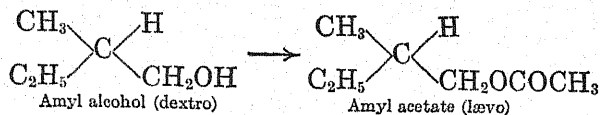


Walden's experiments\* revealed the fact that the weak bases  $\text{Ag}_2\text{O}$ ,  $\text{TlOH}$ ,  $\text{HgO}$ ,  $\text{Hg}_2\text{O}$ , and  $\text{PdO}$  substitute hydroxyl for chlorine in chlorosuccinic acid without change of sign; that is to say, they convert *l*-chlorosuccinic acid into *l*-malic acid. The stronger bases,  $\text{RbOH}$ ,  $\text{KOH}$ ,  $\text{NH}_4\text{OH}$ ,  $\text{Ba}(\text{OH})_2$ ,  $\text{NaOH}$ , and  $\text{LiOH}$ , convert chlorosuccinic acid into malic acid of opposite sign.

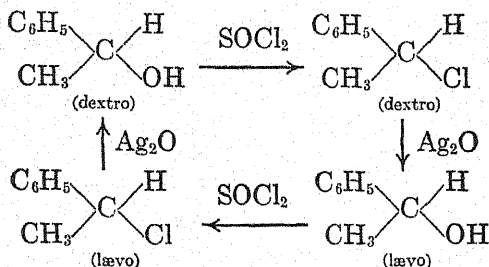
That a change in sign may be produced without altering the relative positions of groups attached to an asymmetric carbon atom, but merely by making a change in the composi-

\* Walden, *Ber.*, 32, 1833 (1899).

tion of one of them, is proved by the fact that dextrorotatory amyl alcohol yields a lævorotatory ester:



Most of the  $\alpha$ -amino acids and some  $\beta$ -amino acids, like the  $\alpha$ -halogen acids, are susceptible to the Walden inversion. Methylphenylcarbinol also undergoes inversion:



Many competent chemists have made systematic investigations of the Walden inversion, and the nature of this rearrangement is now fairly well known. Some of the more important papers relating to the process are listed below.\*

A great variety of mechanisms have been proposed to account for the phenomenon, and a few of these mechanisms will be reviewed, briefly, at this point.

Rørdam assumes that the first step in the process is a dissociation of the asymmetric molecule. He says: "One of the four groups attached to the asymmetric carbon atom is removed, and the remainder of the molecule then oscillates between the two possible extremes corresponding to the *d*- and the *l*-configuration; this continues until the replacing group secures its position in the molecule, so that the resulting configuration of any one molecule is determined by the phase at which the group enters." †

\* Phillips, *J. Chem. Soc.*, 123, 44 (1923). Kenyon, Phillips, and Turley, *J. Chem. Soc.*, 127, 399 (1925). Kenyon and Phillips, *Trans. Farad. Soc.*, 26, 451 (1930). Clough, *J. Chem. Soc.*, 113, 526 (1918). Levene and Marker, *J. Biol. Chem.*, 91, 687 (1931). Levene and Haller, *J. Biol. Chem.*, 83, 185, 591 (1929). Ogg and Polanyi, *Trans. Farad. Soc.* 31, 482 (1935).

† Rørdam, *J. Chem. Soc.*, 1932, 2931. *Ber.*, 67B, 1595 (1934).

The majority of chemists, however, believe that the first step in the process is not a dissociation or ionization of the molecule but the formation of an addition product.

As early as 1911 Werner and Fischer independently suggested that the first step in a substitution process might be the formation of an addition product.\* Their views relating to racemization and inversion may be set forth in connection with a specific example. Let us consider the reaction that occurs when bromopropionic acid reacts with potassium hydroxide. They would say that potassium hydroxide acts upon bromopropionic acid, attaching itself to the asymmetric carbon atom at some place between the four groups satisfying the primary valences of this carbon atom. Potassium bromide is then eliminated. At the moment when the halogen is released from the carbon atom there are two possibilities: (1) the hydroxyl group may take the place vacated by the bromine atom, or (2) it may retain its intermediate position, causing the three remaining groups to shift into new positions to reestablish the tetrahedral form of the molecule. If all molecules behave according to (1), there is no inversion. If all react as indicated in (2), there is total inversion. If half of the molecules react as in (1) and half as in (2), a racemic mixture is produced. Partial racemization always occurs in these reactions, so that any explanation of inversion must present two possible mechanisms.

The view that inversion is caused through the formation of an intermediate addition product was explicitly stated by Lewis in his monograph on Valence. He said: "There seems to be but one possible way of accounting for this peculiar behavior (Walden inversion). Let us consider a carbon atom attached to the four radicals  $R_1$ ,  $R_2$ ,  $R_3$ , and  $R_4$ , and let us assume that a fifth group,  $R_5$ , becomes temporarily attached to the carbon atom near to the face of the tetrahedron which is opposite to  $R_1$ . A slight shift of the kernel might make it now the center of a new tetrahedron with corners at  $R_2$ ,  $R_3$ ,  $R_4$ , and  $R_5$ , while  $R_1$  would become detached from the molecule. Then if the radical  $R_5$  in the new molecules were to be replaced by the radical  $R_1$ , the resulting molecule would be the mirror image of the one with which we started. In this explanation it is not necessary to assume that the five radicals are attached to the carbon for any appreciable period of time, indeed it might be

\* Werner, *Ber.*, 44, 873 (1911). Fischer, *Ann.*, 381, 123 (1911).

assumed that the  $R_1$  leaves at the same instant that the  $R_5$  becomes attached to the carbon atom." \*

Olson has made a precise formulation of the mechanism of the addition reaction and has verified the theory experimentally.† In harmony with the conclusions of Pauling and Slater‡ he assumes that a carbon atom which is exercising its normal valence with atoms attached to the four apexes has a tendency to form other bonds on the faces of the tetrahedron. The stronger the bond is at an apex of the carbon tetrahedron, the weaker will be the tendency for a bond to form on the opposite face of the tetrahedron. If one of the four atoms attached to carbon is easily replaced (is held by a weak bond) the face of the tetrahedron opposite this atom will have a strong tendency to form a bond. As a simple application of this theory we may consider the reaction between methyl chloride and potassium hydroxide. It is assumed that the hydroxyl group becomes attached to the carbon atom on the center of the face of the tetrahedron opposite the apex to which the chlorine is attached. The chlorine atom then leaves the carbon, as chloride ion, and the carbon atom assumes a new configuration, an apex being formed at the position of the hydroxyl group. The hydroxyl group does not occupy the position that was vacated by the chlorine atom but is in a position exactly opposite the place originally occupied by the chlorine atom. The group which is to be displaced determines a unique path for the entering group. This leads to an inversion of the configuration of the molecule with respect to the carbon atom on which the substitution has occurred.

This theory can be applied to every known case of optical inversion, but its usefulness as a means of predicting results is impaired by the fact that the solvent or even the walls of the container may in some cases take part in the formation of an addition product. Under such circumstances it is impossible to determine the number of steps (and, therefore, the number of inversions) that are involved in a substitution process.

The course of a substitution reaction may be modified by the solvent, the temperature, the nature of the walls of the con-

\* G. N. Lewis, *Valence and the Structure of Atoms and Molecules*, p. 118. Reinhold Publishing Corp., N. Y.

† A. R. Olson, *J. Chem. Phys.*, **1**, 418 (1933).

‡ Pauling, *J. Am. Chem. Soc.*, **53**, 1367 (1931). J. C. Slater, *Phys. Rev.*, **37**, 481 (1931).

tainer, and by other factors. Such processes are seldom as simple and direct as stoichiometric equations imply. In an investigation of the reaction between *l*-bromosuccinic acid and chloride ion Olson and Long found that the exchange of chlorine for bromine was only one of a large number of simultaneous reactions.\* They were able to suppress lactone formation and hydrolysis to such an extent that only six reactions occurred at appreciable rates. A quantitative study of the rates of these six reactions was made. Then, under the assumption that substitution is accomplished through the formation of an addition product and that complete structural inversion occurs when an addition product is formed, they calculated the rotation that a solution of bromosuccinic acid and hydrochloric acid should have at various intervals of time after mixing the reagents. The agreement between the theoretical and the experimental values was remarkable.

This mechanism of addition and inversion does not apply to substitution processes that occur through preliminary ionization of the reagents, but it seems to apply to most substitution processes in which at least one of the reacting substances is a nonelectrolyte.

\* Olson and Long, *J. Am. Chem. Soc.*, 56, 1294 (1934).

## APPENDIX

### FORMULAS

From analytical data the simplest empirical formula of a compound may be calculated. The relative weights of the elements found in a compound divided by their respective atomic weights must give the numerical ratios in which the atoms of the different elements exist in the molecule. A substance, for example, has the composition: carbon, 40 per cent; hydrogen, 6.6 per cent; oxygen, 53.3 per cent. The atoms of carbon, hydrogen, and oxygen in the molecule must be associated in the ratio  $\frac{40.0}{12} : \frac{6.6}{1} : \frac{53.3}{16}$  or 3.3 to 6.6 to 3.3. Since, from the law of multiple proportion, we conclude that molecules do not contain fractional parts of atoms we must express these ratios in whole numbers. The smallest whole numbers representing these relative values are 1:2:1 and hence the simplest empirical formula for the compound is  $\text{CH}_2\text{O}$ . The same ratios are expressed, however, by the formulas  $\text{C}_2\text{H}_4\text{O}_2$ ,  $\text{C}_3\text{H}_6\text{O}_3$ ,  $\text{C}_6\text{H}_{12}\text{O}_6$ , or, in general,  $\text{C}_n\text{H}_{2n}\text{O}_n$ . All of these formulas correspond to the composition indicated above. In order to determine which formula should be assigned to the substance under investigation we must know its molecular weight. Formaldehyde (mol. wt. 30) has the formula  $\text{CH}_2\text{O}$ . Acetic acid (mol. wt. 60) has the formula  $\text{C}_2\text{H}_4\text{O}_2$ . Lactic acid is  $\text{C}_3\text{H}_6\text{O}_3$  and glucose is  $\text{C}_6\text{H}_{12}\text{O}_6$ . The best methods for estimating molecular weights are based upon the gas laws and upon principles relating to the properties of solutions.

### MOLECULAR WEIGHTS FROM PROPERTIES OF GASES

Vapor density methods are usually employed in determining the molecular weights of all compounds that vaporize without decomposition. According to Avagadro's law, equal volumes of all gases at the same temperature and pressure contain the same number of molecules. In other words the molecular weights of all gases under identical conditions of temperature and pressure occupy the same volume. At  $0^\circ\text{C}$ . and 760 mm. pressure the gram molecular volume is 22.4 liters. The molecular weight of a substance is, therefore, the weight of 22.4 liters of its vapor under standard conditions.



A convenient formula for calculating molecular weights may be derived from the gas laws as follows:

Begin with one mol of gas occupying volume  $v$  at pressure  $p$  and temperature  $T$ . Suppose the pressure is changed from  $p$  to  $p'$ ; the volume will change to some new value  $V$ . From Boyle's law

$$pv = p'V \quad \text{and} \quad V = \frac{pv}{p'} \quad (1)$$

Now, keeping the pressure constant at  $p'$ , let the temperature be changed to  $T'$ . The volume will again be changed; this time from  $V$  to  $v'$ ; and from Charles's law

$$\frac{V}{T} = \frac{v'}{T'} \quad \text{or} \quad V = \frac{v'T'}{T}; \quad (2)$$

equating the equal values of  $V$  in (1) and (2) we have

$$\frac{pv}{p'} = \frac{v'T'}{T} \quad (3)$$

Multiplying both sides of this equation by  $p'$  and dividing by  $T'$  we obtain the equation

$$\frac{pv}{T} = \frac{p'v'}{T'} \quad (4)$$

That is to say, the value of  $\frac{pv}{T}$  is a constant quantity. The gas constant is usually represented by  $R$  and the equation is written

$$\frac{pv}{T} = R \quad \text{or} \quad pv = RT. \quad (5)$$

Substituting for  $T$  the absolute temperature, for  $p$  the pressure in atmospheres, and for  $v$  the volume in liters occupied by a mol of gas under these conditions, we obtain the numerical value 0.082 for the constant  $R$ .\*

To make the equation general, an additional factor must be introduced, namely,  $n$ , the number of mols or the fractional part of a mol measured. The expression then becomes

$$pv = nRT. \quad (6)$$

\* The numerical value of the gas constant,  $R$ , depends upon the units employed in pressure and volume measurements.

| $P$                    | $V$    | $R$                |
|------------------------|--------|--------------------|
| atmospheres            | liters | 0.0821             |
| atmospheres            | cc.    | 82.1               |
| mm. Hg.                | cc.    | 62360              |
| dynes/cm. <sup>2</sup> | cc.    | $8.31 \times 10^7$ |

One calorie is equivalent to  $4.18 \times 10^7$  ergs; hence in units of heat capacity  $R = \frac{8.31}{4.18} = 1.99$  cal. or, approximately, 2.

We may substitute for  $n$  the ratio  $\frac{W}{M}$  in which  $W$  is the weight of the gas measured and  $M$  its molecular weight.

$$\text{Then} \quad pv = \frac{WRT}{M} \quad \text{or} \quad M = \frac{WRT}{pv}. \quad (7)$$

Many practical methods for determining the values required in this equation have been devised. In dealing with the permanent gases it is only necessary to weigh an evacuated flask of known volume and weigh again after filling it with the gas at atmospheric pressure and room temperature. For volatile liquids the Victor Meyer method is convenient but lacks precision. A weighed sample of the liquid under investigation is sealed in a small glass bulb,  $G$  (Fig. 1), which rests on a rod,  $E$ , in the upper end of a long glass tube,  $A$ . An air-tight rubber connection is made between the rod  $E$  and the side arm of the tube. The tube  $A$  is heated to a temperature above the boiling point of the sample in  $G$  by the vapor of a liquid which is kept boiling in the outer jacket  $B$ . After the tube  $A$  has acquired the temperature of the vapor bath surrounding it, an air-tight stopper is inserted in the top of tube  $A$ , then the sample is dropped from the detent by pulling out on the rod  $E$ . The rubber connection stretches enough to let the bulb fall. On striking the bottom of  $A$  the capillary end of the bulb is broken and the sample immediately vaporizes forcing an equivalent volume of air into the eudiometer  $D$ , which at the beginning of the experiment is filled with water. Since all gases have practically the same coefficient of expansion the volume of air received by the eudiometer represents the volume that the weighed sample would occupy if it could exist as a vapor at the temperature of the room under atmospheric pressure. The variables  $P$ ,  $W$ , and  $T$  are fixed in advance by the conditions of the experiment and  $V$  is measured.

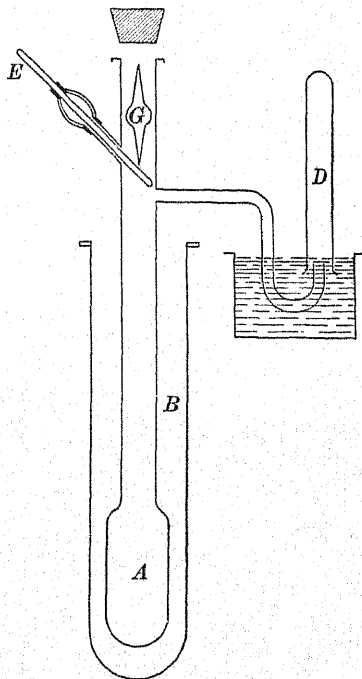


FIG. 1

According to the method of Chapin a weighed sample is evaporated in an apparatus of known volume and the change in pressure is measured.<sup>1</sup>

The temperature,  $T$ , is the variable measured in the method<sup>2</sup> represented in Fig. 2. The volume of the glass bulb  $A$  from the capillary at  $C$  to the point marked  $E$  is accurately determined. Platinum wires are sealed into the stem of the bulb at  $E$  and  $F$ . These wires are connected with the poles of a battery,  $B$ , through the relay  $R$ . Mercury is poured into the reservoir  $G$  until the surface of the

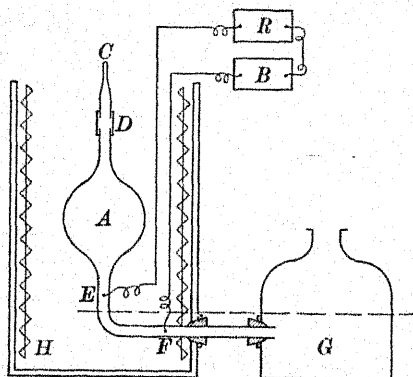


FIG. 2

mercury makes contact with the platinum point at  $E$ . A small thin walled glass bulb containing a weighed sample of the liquid is introduced into  $A$ . A short glass tube with one end ground to fit the neck of the flask and the other end drawn out to a capillary is connected by means of heavy rubber tubing to the upper end of  $A$ . By means of compressed air mercury is forced from the reservoir into  $A$  until it rises to the top of the capillary

at  $C$ . The end of the capillary is then sealed. The oil bath surrounding  $A$  is heated by means of an electric current passing through coils of nichrom wire. The current is turned on and off automatically through the operation of the relay  $R$ . The capillary end of the sample tube is broken off by bending the rubber joint at  $D$  and the sample is thereby released on the surface of the mercury. As the specimen vaporizes mercury is forced back into the reservoir. The temperature of the bath is raised until the vapor fills the bulb to the point  $E$ . The break in contact between the mercury and the platinum point is indicated by the relay, and at the same time the current is turned off from the heating coils,  $H$ , in the oil bath. Due to a lag in the temperature of the vapor, the mercury level continues to fall for a short time after the heat is turned off; but as the oil bath cools the mercury rises. When contact with the platinum is made again the heat is turned on automatically, and within fifteen or twenty minutes the "make and break" of contact correspond to changes of only one or two tenths of a degree

<sup>1</sup> Chapin, *J. Phys. Chem.*, **22**, 337 (1918).

<sup>2</sup> Porter, *J. Am. Chem. Soc.*, **34**, 1290 (1912).

in the temperature of the oil bath. The mercury now stands at the same level in both sides of the apparatus, and the temperature at which the known weight of substance fills a given volume at atmospheric pressure is observed.

### MOLECULAR WEIGHTS FROM PROPERTIES OF SOLUTIONS

Many compounds decompose when heated and cannot be obtained in the vapor state. Methods based upon the gas law cannot be used in such cases. Raoult's discovery that the lowering of the vapor pressure of a solvent by a dissolved substance is determined by the relative number of molecules of solute and of solvent in any solution, and is independent of the mass of the dissolved molecule, gives a means of estimating the molecular weight of a dissolved substance by vapor pressure measurement or by the measurement of any definite function of the change in vapor pressure such as osmotic pressure, freezing point lowering, or elevation of boiling point.

### VAPOR PRESSURE

The vapor pressure of pure water at 20° is sufficient to support a column of mercury 17.36 mm. high. In a solution containing one mol of sugar and seventy mols of water the mol fraction of water is 70/71 and the vapor pressure of the solution at 20° is

$$70/71 \times 17.36 = 17.11 \text{ mm.}$$

The vapor pressure of the solvent is proportional to its mol fraction in the solution. The lowering of the vapor pressure (in this case 1/71 of the original value) is proportional to the mol fraction of the solute. In general terms Raoult's law is written  $\frac{p_0 - p}{p_0} = \frac{n}{N + n}$

where  $p_0$  and  $p$  are the vapor pressures of the pure solvent and of the solution respectively,  $N$  is the number of mols of the solvent, and  $n$  is the number of mols of the solute. Or  $p = p_0 X_0$  if  $X_0$  is the mol fraction of the solvent in the solution. In the pure solvent  $X_0 = 1$ .

In very dilute solutions  $n + N$  does not differ appreciably from  $N$ ; and, representing  $p_0 - p$  by the symbol  $\Delta p$ , we have

$$\frac{\Delta p}{p_0} = \frac{n}{N}.$$

### BOILING POINT AND FREEZING POINT

The curve  $BC$  (Fig. 3) represents the vapor pressure of a pure liquid between its freezing point and boiling point. The vapor pressure of the solid phase is indicated by  $AB$ . The curve  $DE$  represents the vapor pressure of a solution. As the temperature rises the

vapor pressure of the pure solvent or of any solution increases until it reaches a value equal to atmospheric pressure. The liquid then boils at constant temperature. Boiling point may be defined as the temperature at which the vapor pressure of the liquid is equal

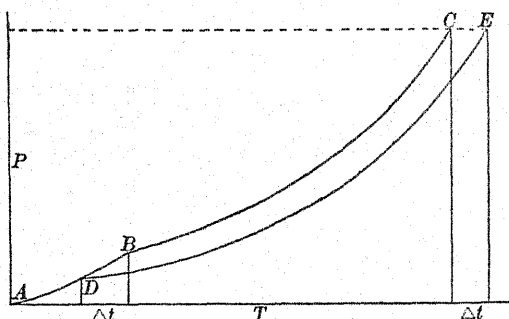


FIG. 3

to the pressure of the atmosphere resting upon its surface. The freezing point is the temperature at which the liquid and solid phases have the same vapor pressure. Since the vapor pressure of a solvent is lowered by dissolved molecules, the boiling point of a solution

must be higher and the freezing point lower than the corresponding points for the pure solvent. The elevation of the boiling point or depression of the freezing point is represented by the symbol  $\Delta t$ .

When one mol of any substance, which does not dissociate nor associate in solution, is dissolved in 1000 grams of water the freezing point is lowered  $1.86^\circ$  and the boiling point is elevated  $0.52^\circ$ . For any quantity of solute in 1000 grams of water  $\Delta t = 1.86 \times \frac{W}{M}$ , if  $W$  is the weight of dissolved substance and  $M$  its molecular weight. Representing the weight of water used by  $G$ , an additional factor,  $\frac{1000}{G}$ , may be introduced to indicate the effect of changing the concentration of the solution by varying the amount of solvent used.

$$\text{Then} \quad \Delta t = 1.86 \times \frac{W}{M} \times \frac{1000}{G}.$$

Substituting  $K$  for the product of the two constants,

$$M = \frac{KW}{G\Delta t}.$$

#### VALUES OF $K$ FOR VARIOUS SOLVENTS

| SOLVENT               | F. P. CONST. | B. P. CONST. |
|-----------------------|--------------|--------------|
| Water . . . . .       | 1863         | 520          |
| Acetic acid . . . . . | 3860         | 260          |
| Benzene . . . . .     | 5000         | 328          |
| Ether . . . . .       | —            | 300          |

It will be observed that  $K$  is the theoretical value of  $\Delta t$  for a solution containing one mol of solute per gram of solvent.  $K$  may be calculated from the heat of vaporization,  $L$ , and the absolute temperature,  $T$ , at which the solvent is vaporized, or from the heat of fusion,  $L$ , and the temperature,  $T$ , at which the pure solvent melts:

$$K = \frac{RT^2}{L}.$$

Thus for water,

$$K_B = \frac{2 \times (373)^2}{537} = 520,$$

and

$$K_F = \frac{2 \times (273)^2}{80} = 1863.$$

A definite relationship existing between changes in boiling point and molal concentration of a solution is expressed in the equation

$$\Delta t = \frac{RT^2}{L} \cdot \frac{n}{N+n},$$

or

$$\Delta t = kx.$$

In this equation  $L$  is the heat of vaporization or heat of fusion of one mol (not one gram) of the solvent; hence  $k$  is equal to  $K$  (page 464) divided by the molecular weight of the solvent, and  $x$  is the mol fraction of the solute.

#### VALUES OF $k$ FOR VARIOUS SOLVENTS

| SOLVENT               | F. P. CONST. | B. P. CONST. |
|-----------------------|--------------|--------------|
| Water . . . . .       | 104          | 29           |
| Acetic acid . . . . . | 64.3         | 4.3          |
| Benzene . . . . .     | 64.1         | 4.2          |
| Ether . . . . .       | —            | 4.1          |

#### OSMOTIC PRESSURE

The osmotic pressure of a solution is definitely related to the lowering of the vapor pressure caused by the dissolved substance. Therefore, the mol fraction of a solute and its molecular weight may be determined from osmotic pressure measurements.

If in an inclosed space (Fig. 4) a solution,  $l$ , be separated from the pure solvent,  $s$ , by means of a semi-permeable membrane,  $m$ , pure solvent will pass through the membrane in one direction or the other until equilibrium is reached, that is, until the solution has such concentration that its osmotic pressure is exactly equal to the weight of the column of solvent supported. Let the height of this column be  $h$ . Now, the vapor pressure of the solution,  $l$ , must be

exactly equal to the pressure of the vapor of the pure solvent in the saturated atmosphere at the same level; that is, at the distance  $h$

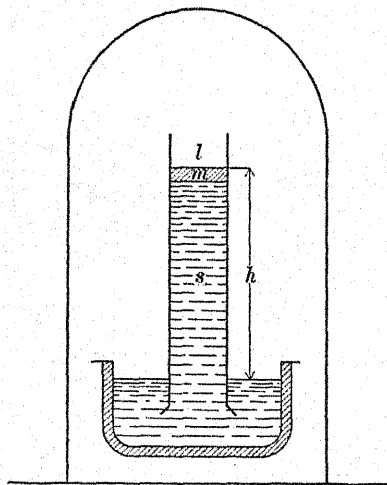


FIG. 4

above the surface of the solvent. Any inequality in these values would result in perpetual motion, the solvent continually moving through the membrane in one direction with a corresponding movement of the vapor in the opposite way. The difference between the vapor pressure of the solvent and solution corresponds, therefore, to the difference between the pressures of the vapor of the solvent at the levels of the two liquid surfaces  $h$  cm. apart. The change in pressure,  $dp$ , corresponding to a small change in elevation above the surface of the solvent is determined by

the density,  $D$ , of the vapor in that region and the magnitude of the change in altitude,  $dh$ :

$$dp = Ddh. \quad (1)$$

$$\text{From the gas laws we have } pv = \frac{WRT}{M} \quad (\text{p. 465}); \quad (2)$$

$$\text{then} \quad p = \frac{W}{v} \cdot \frac{RT}{M} \quad \text{and} \quad \frac{W}{v} = \frac{Mp}{RT}. \quad (3)$$

$$\text{But} \quad \frac{W}{v} = D, \text{ the density of the vapor};$$

$$\text{hence} \quad p = \frac{RTD}{M} \quad \text{and} \quad D = \frac{Mp}{RT}. \quad (4)$$

Substituting this value of  $D$  in (1),

$$dp = \frac{Mp}{RT} dh \quad \text{or} \quad \frac{dp}{p} = \frac{M}{RT} dh. \quad (5)$$

Integrating between the values of  $p_0$  and  $p$ , the vapor pressures of the solvent and solution respectively,

$$\log \frac{p_0}{p} = \frac{Mh}{RT} \quad \text{or} \quad h = \frac{RT}{M} \log \frac{p_0}{p}. \quad (6)^*$$

We now have the height of the column of solvent in terms of the molecular weight,  $M$ , of the solvent, the temperature,  $T$ , and the

\* Natural logarithms.

vapor pressures of solvent and solution. The osmotic pressure,  $P_{os}$ , is equal to the height of the column,  $h$ , multiplied by the density,  $D_0$ , of the solvent.

$$P_{os} = hD_0.$$

Then

$$P_{os} = \frac{RTD_0}{M} \log \frac{p_0}{p}. \quad (7)$$

This equation is quite exact over any range of concentration if the vapor of the solvent obeys the gas law.

According to Raoult's law,

$$\log \frac{p_0}{p} = \log \frac{N+n}{N} = \log \left( \frac{n}{N} + 1 \right).$$

Expanding this into a powers series,

$$\log \left( \frac{n}{N} + 1 \right) = \frac{n}{N} - \frac{1}{2} \left( \frac{n}{N} \right)^2 + \frac{1}{3} \left( \frac{n}{N} \right)^3 \dots$$

In dilute solutions  $\frac{n}{N}$  is a small fraction and the higher powers of the fraction become negligible. Assuming that all terms except the first may be neglected for dilute solutions, we have

$$P_{os} = \frac{RTD_0}{M} \cdot \frac{n}{N}.$$

The product,  $MN$ , is the weight of the solvent (mol. wt. times the number of mols) and  $D_0$  is its density,

therefore

$$\frac{D_0}{MN} = \frac{1}{V_0}$$

and

$$P_{os} = \frac{nRT}{V_0}, \quad (8)$$

where  $V_0$  is the volume of the pure solvent. This is the well-known Morse and Fraser equation. By making one more approximation, namely, that the solvent and solution have the same density, which is true only at infinite dilution, we obtain the van't Hoff equation,

$$P_{os} = \frac{nRT}{V}, \quad (9)$$

in which  $V$  is the volume of the solution.

Van't Hoff developed the equation in an empirical way from observations leading to the conclusion that dissolved substances obey the gas laws. It is true that the osmotic pressure of a dilute solution varies as the absolute temperature (Charles' law) and is proportional to the number of mols of solute per unit volume (Boyle's law), but the nature of osmotic pressure is totally different from that of an effect produced by the bombardment of the walls of a vessel by gas molecules.



It must be remembered that the methods given above for molecular-weight determinations are based upon the assumption that the vapors obey the gas laws, and that solutions act in accord with Raoult's law. In actual experience a perfect gas is never found; and a solution that shows no deviations from the laws of perfect solutions is never encountered. Hence, molecular-weight determinations are inexact. In most cases, however, such determinations are used as a basis for deciding whether a compound should be represented by its simplest empirical formula or some multiple of this value. The methods are good enough to serve this purpose.

## QUESTIONS AND PROBLEMS

1. The formula for methane is  $\text{CH}_4$ . Calculate the weight of 1 liter of the gas at  $0^\circ \text{C}$ . and 760 mm.

2. From the formula of ethane calculate the weight of 1 liter of the gas at  $0^\circ$  and 760 mm. and at  $30^\circ$  and 680 mm.

3. Calculate the volume of 15 g. of ethane at  $40^\circ$  and 640 mm.

4. A compound is 24 per cent carbon; what is the lowest possible molecular weight the compound can have?

5. A compound composed of hydrogen and carbon was oxidized by heating it with copper oxide. The hydrogen of the compound was converted into water and the carbon into carbon dioxide. From the following data calculate the percentage of each element in the compound:

Weight of sample . . . . . 0.40 g.

Weight of water formed . . . . . 0.90 g.

Weight of carbon dioxide . . . . . 1.10 g.

6. A substance composed of carbon, hydrogen, and oxygen was analyzed. From the following data calculate its composition:

Weight of sample . . . . . 0.2046 g.

Weight of water formed . . . . . 0.1255 g.

Weight of carbon dioxide . . . . . 0.2985 g.

7. Assuming that the compound referred to in problem 6 has a molecular weight of 210, write its molecular formula.

8. Write the simplest formula that represents a compound having the following composition:

Carbon . . . . . 40.00 %

Hydrogen . . . . . 6.66 %

Oxygen . . . . . 53.33 %

9. If the compound referred to in problem 8 has a molecular weight of 180, what is its molecular formula?

10. A compound has the following composition:

Carbon . . . . . 62.05 %

Hydrogen . . . . . 10.35 %

Oxygen . . . . . 27.60 %

At  $20^\circ$  and 760 mm. 1.12 liters of its vapor weighs 2.7 g. Write the formula of the compound. (See Appendix for methods of determining molecular weights.)

11. A sample of a substance weighing 0.304 g. gave upon combustion 0.430 g. of carbon dioxide and 0.2626 g. of water. The sulfur in a sample of the same substance was converted into barium sulfate, and 0.246 g. of the

substance gave 0.924 g. of barium sulfate. What is the empirical formula of the substance?

12. How many cubic centimeters of nitrogen measured at  $30^{\circ}$  and 740 mm. may be obtained from 0.152 g. of a compound having the molecular formula  $C_6H_7N$ ?

13. A compound which contained nitrogen was analyzed with the following results: 0.728 g. of the substance gave 68 cc. of nitrogen measured at  $20^{\circ}$  and 750 mm. pressure. Calculate the percentage of nitrogen in the compound.

14. When 1.50 g. of a substance was dissolved in 40 g. of water, the freezing point was lowered  $0.11^{\circ}$ . Calculate the molecular weight of the compound.

15. A hydrocarbon was analyzed with the following results:

|   |          |
|---|----------|
| Weight of sample . . . . .                  | 0.280 g. |
| Weight of carbon dioxide produced . . . . . | 0.880 g. |
| Weight of water formed . . . . .            | 0.360 g. |

The vapor density of the compound was measured by the Victor Meyer method. A sample weighing 0.1470 g. displaced 43.2 cc. of air measured at  $20^{\circ}$  and 740 mm. Write its molecular formula. (See Appendix for the Victor Meyer method of determining molecular weights.)

16. A compound of carbon and hydrogen was analyzed with the following results: 0.420 g. of the substance gave 1.320 g. of  $CO_2$  and 0.540 g. of  $H_2O$ . In a determination of the molecular weight by the Victor Meyer method 0.337 g. of the vaporized substance displaced 100 cc. of air at  $20^{\circ}$  and 740 mm. pressure. Calculate the molecular formula of the substance.

17. List the following gases in the order of increasing density:  $C_2H_6$ , CO,  $NH_3$ ,  $CH_4$ ,  $C_2H_2$ . What is the weight of 22.4 liters of each of these gases at  $0^{\circ}C$ . and 760 mm.?

18. Is a mixture of air and gasoline vapor heavier or lighter than air alone? What is the basis of your conclusion?

19. Write the structural formulas of the hydrocarbons of the composition  $C_5H_{10}$ . Name each as a derivative of ethylene.

20. Outline methods for detecting the presence of carbon and hydrogen in organic compounds. Explain each test.

21. Outline qualitative tests for sulfur and nitrogen in organic compounds. How are the same elements estimated quantitatively?

22. A mixture of oxygen and ethane at  $20^{\circ}$  measured 110 cc. The mixture was exploded by means of an electric spark. After the products cooled to room temperature, the volume was 60 cc. After the carbon dioxide had been removed by treatment with potassium hydroxide solution, the residual gas, which was oxygen, occupied 20 cc. Find the percentage of ethane in the original mixture.

23. What volume of pure oxygen is required to burn 1 liter of ethane?

24. What weight of oxygen is required to burn 10 g. of ethane?

25. What volume of air is required to burn 1 liter of methane? What volume of carbon dioxide would be formed? Assume that the methane, air,

and carbon dioxide are measured under the same conditions of temperature and pressure.

26. A mixture of hydrogen, nitrogen, and methane was exploded with a measured volume of oxygen. The residual gas was shaken with a saturated solution of potassium hydroxide. All gas measurements were made under atmospheric pressure and at a constant temperature. From the following data calculate the percentages, by volume, of the three gases in the original mixture:

|   |        |
|---|--------|
| Volume of mixed gases . . . . .   | 40 cc. |
| Volume of oxygen added . . . . .  | 80 cc. |
| Volume after explosion . . . . .  | 56 cc. |
| Volume after absorption of carbon dioxide by a solution<br>of potassium hydroxide . . . . . | 36 cc. |

27. Devise a means of estimating the quantity of each gas present in a mixture of methane, nitrogen, and carbon dioxide.

28. How could you determine the percentage by volume of each gas in mixtures of (a) ethylene and ethane? (b) methane, ethylene, and nitrogen?

29. How could you distinguish from one another (a) propane, propene, and propine? (b) ethylacetylene and dimethylacetylene?

30. How would you estimate the quantity of ethane, ethylene, and acetylene in a mixture of the three gases?

31. Write a graphic formula for each of three compounds having the formula  $C_4H_8$ .

32. Write the structural formulas of the hexanes, and name them.

33. Calculate the heats of formation (a) of propane, (b) of propylene, (c) of acetylene.

34. Write structural formulas for the products formed when ethylene reacts (a) with  $Br_2$ , (b) with  $H_2SO_4$ , (c) with  $HI$ , (d) with  $HOCl$ .

35. A hydrocarbon gas combines directly with an equal volume of chlorine gas. The addition product has a molecular weight of 127. What is the molecular formula of the original gas?

36. Write the formulas of the monobromopropanes, and name them.

37. How would you estimate the quantity of alcohol in a mixture of ethyl alcohol and hexane?

38. A saturated alcohol having the formula  $C_8H_{18}O$  is converted by acetyl chloride into a compound having the formula  $C_8H_{14}O_2$ . Write a structural formula for each of these compounds.

39. Write structural formulas for all alcohols having the formula  $C_6H_{11}OH$ . Name each as a derivative of methyl alcohol (carbinol).

40. Write the structural formulas of the amyl alcohols, and name each according to the Geneva system.

41. Two grams of a monohydric alcohol, when treated with metallic sodium, liberated 374 cc. of hydrogen gas at standard conditions. What is the molecular weight of the alcohol?

42. How could you distinguish by chemical tests (a) ethyl alcohol and hexane? (b) ethyl alcohol and methyl alcohol? (c) tertiary butyl alcohol and acetone? (d) isoamyl alcohol and isopropyl alcohol?

43. Write equations for reactions by which propylene glycol can be prepared from propylene.

44. What volume of ethylene, at 25° and 760 mm. pressure, should be obtained from 2 lb. of 95 per cent alcohol?

45. Outline a method for the separation of *n*-hexane and methyl alcohol.

46. Write an equation representing a reaction of *n*-butyl alcohol with acetyl chloride.

47. Write the structural formulas of the hexyl alcohols, and name each.

48. Write the formulas for the possible heptanols.

49. Show how propylene glycol,  $\text{CH}_3\text{—CHOH—CH}_2\text{OH}$ , may be made from propyl alcohol.

50. How would you accomplish the complete removal of water and alcohol from ether?

51. A mixture of alcohol and concentrated  $\text{H}_2\text{SO}_4$  contains ethyl sulfuric acid. How could you employ this mixture to prepare (a) ethylene? (b) ether? How do the experimental conditions differ in the two cases? Write equations for both processes.

52. How would you prepare ethylene from  $\text{CH}_3\text{CH}_2\text{OH}$ ? from  $\text{CH}_3\text{CH}_2\text{I}$ ? from  $\text{CH}_2\text{BrCH}_2\text{Br}$ ? How would you prepare each of these compounds from ethylene?

53. Calculate the weight of ethyl bromide that may be prepared from 60 g. of alcohol through the agency of phosphorus tribromide.

54. Write equations for reactions of ethyl alcohol with (a)  $\text{H}_2\text{SO}_4$ , (b)  $\text{CH}_3\text{COCl}$ , (c) Na, (d)  $\text{PCl}_3$ .

55. Write the graphic formulas of the alcohols having the composition  $\text{C}_6\text{H}_{13}\text{OH}$ . Which of these alcohols contain an asymmetric carbon atom?

56. How would you separate and identify the components of a mixture of ammonium chloride and methylamine hydrochloride?

57. What compounds exist in a dilute water solution of ethylamine and acetic acid?

58. Outline a method for making trimethylbutylammonium hydroxide.

59. Two compounds have the formula  $\text{C}_2\text{H}_5\text{NO}_2$ . On reduction one yields an alcohol and the other an amine. Assign to each a graphic formula.

60. What volume of nitrogen gas, under standard conditions, would be evolved if 3 g. of methyl ammonium nitrate were treated with nitrous acid?

61. Two compounds have the formula  $\text{C}_3\text{H}_5\text{N}$ . Nitrous acid converts one of them into  $\text{C}_3\text{H}_5\text{O}$  and the other into  $\text{C}_3\text{H}_5\text{N}_2\text{O}$ . Write a graphic formula for each of the four compounds.

62. A yield of 12 g. of acetone was obtained in the dry distillation of 65 g. of calcium acetate. What percentage is this of the theoretical yield?

63. A sample of a mixture of alcohol and acetaldehyde weighing 0.30 g. precipitated 0.75 g. of cuprous oxide from Fehling's solution. What was the percentage of aldehyde in the mixture?

64. Write the formulas for the phenylhydrazones of propionaldehyde and butyraldehyde.

65. Show by what chemical reactions the following groupings of atoms can be obtained: (a)  $\text{RCH} : \text{CHBr}$ , (b)  $\text{R}_2\text{CBr}_2$ , (c)  $\text{R} \cdot \text{O} \cdot \text{R}$ , (d)  $\text{R}-\text{CO}-\text{R}$ .

66. An organic substance with the empirical formula  $\text{C}_4\text{H}_{10}\text{O}$  was converted by  $\text{PCl}_5$  into  $\text{C}_4\text{H}_9\text{Cl}$ . The original substance was changed by  $\text{K}_2\text{Cr}_2\text{O}_7$  and  $\text{H}_2\text{SO}_4$  into a ketone,  $\text{C}_4\text{H}_8\text{O}$ . What was the substance? Write equations to represent all the reactions involved in the identification.

67. Starting with *n*-butyl magnesium bromide, outline the preparation of dimethyl *n*-butyl carbinol.

68. Starting with acetone, show by equations how the following may be made: (a)  $(\text{CH}_3)_2\text{C}_2\text{H}_5 \cdot \text{COH}$ , (b)  $\text{CH}_3\text{CBr} : \text{CH}_2$ , (c)  $(\text{CH}_3)_2\text{C} : \text{CH}_2$ .

69. Show how you could separate the components of the following mixtures without the use of distillation:

- (a)  $\text{C}_5\text{H}_{11}\text{CHO}$  and  $\text{C}_6\text{H}_{14}$ ,
- (b)  $(\text{CH}_3)_2\text{CO}$  and  $\text{C}_2\text{H}_5\text{OH}$ ,
- (c)  $(\text{C}_2\text{H}_5)_2\text{O}$  and  $\text{CH}_3\text{COC}_2\text{H}_5$ .

70. Acetic acid is only about 1 per cent ionized in a 0.1 *N* solution, yet a gram-molecule of acetic acid is capable of neutralizing as much alkali as is a gram-molecule of hydrochloric acid which is completely ionized under the same conditions. Explain.

71. A substance with molecular weight 62 reacts with acetyl chloride to form hydrochloric acid and a liquid which on purification proves to have the molecular formula  $\text{C}_6\text{H}_{10}\text{O}_4$ . Write the structural formula of the original substance.

72. Starting with glycerine, show how  $\beta$ -iodopropionic acid may be made.

73. Starting with acetylene, outline a possible synthesis of (a) acetone, (b) ethyl alcohol, (c) tertiary butyl alcohol, (d) methylamine, (e) isopropyl alcohol.

74. The acid number is defined as the number of milligrams of potassium hydroxide required to neutralize 1 g. of a substance. Calculate the acid number of stearic acid.

75. One mole of an ester is shaken with one mole of water until no further change occurs. What products are present in the mixture thus produced? How would the relative amounts of each product be changed by the addition of (a) anhydrous calcium chloride? (b) sodium hydroxide?

76. A neutral sample of crude ethyl acetate weighing 0.50 g. was boiled with 30 cc. of 0.2 *N* alcoholic potash. For back titration 15.0 cc. of 0.1 *N* acid was required. What was the percentage of ester in the sample?

77. How could you convert an acid into an acid chloride? an acid chloride into an ester? a nitro compound into an amine? an amine into an alcohol? an ester into an amide?

78. Outline methods for distinguishing the members of the following pairs of compounds; do not use tests involving analyses, melting points, boiling points, or molecular-weight measurements:

- (a)  $\text{CH}_3\text{COCH}_3$  and  $\text{CH}_3\text{CH}_2\text{CHO}$ ,
- (b)  $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$  and  $\text{CH}_3\text{CHOHCH}_3$ ,
- (c)  $\text{CH}_3\text{OCH}_3$  and  $\text{CH}_3\text{CH}_2\text{OH}$ ,
- (d)  $\text{RCH}_2\text{Cl}$  and  $\text{RCOCl}$ ,
- (e)  $\text{CH}_3\text{COC}_2\text{H}_5$  and  $\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$ .

79. A compound has the composition and molecular weight represented by the formula  $\text{C}_4\text{H}_8\text{O}_2$ . It reacts with acetyl chloride, forming a compound corresponding to the formula  $\text{C}_6\text{H}_{10}\text{O}_3$ . It forms an addition product with sodium hydrogen sulfite, and it is easily oxidized to acetic acid. Write its structural formula.

80. Specify the reagents and the experimental conditions required to make the following conversions:

- (a)  $\text{CH}_3\text{NH}_2$  to  $\text{CH}_3\text{OH}$ ,
- (b)  $\text{CH}_3\text{OH}$  to  $\text{CH}_3\text{Br}$ ,
- (c)  $\text{CH}_2=\text{CH}_2$  to  $\text{CH}_3\text{CH}_2\text{I}$ ,
- (d)  $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$  to  $\text{CH}_3\text{CHOHCH}_3$ ,
- (e)  $\text{CH}_4$  to  $\text{CH}_3\text{COOH}$ ,
- (f)  $\text{CH}_3\text{COOH}$  to  $\text{CH}_4$ ,
- (g)  $\text{CH}_3\text{CH}_2\text{I}$  to  $\text{CH}_2=\text{CH}_2$ ,
- (h)  $\text{CH}_3\text{CONH}_2$  to  $\text{CH}_3\text{NH}_2$ .

81. Outline chemical tests that may be used to distinguish between the members of the following pairs of compounds:

- (a)  $\text{C}_2\text{H}_5\text{NH}_2$  and  $\text{CH}_3\text{CONH}_2$ ,
- (b)  $(\text{C}_2\text{H}_5)_2\text{O}$  and  $\text{C}_2\text{H}_5\text{COOC}_2\text{H}_5$ ,
- (c)  $(\text{CH}_3)_2\text{O}$  and  $\text{CH}_3\text{CH}_2\text{OH}$ ,
- (d)  $\text{CH}_3\text{COCH}_3$  and  $\text{CH}_3\text{CH}_2\text{OH}$ ,
- (e)  $\text{C}_2\text{H}_5\text{Cl}$  and  $\text{CH}_3\text{COCl}$ ,
- (f)  $\text{CH}\equiv\text{C}-\text{C}_2\text{H}_5$  and  $\text{CH}_3\text{C}\equiv\text{C}-\text{CH}_3$ .

82. Indicate chemical reactions that may be used to distinguish between

- (a)  $\text{CH}_2=\text{CH}_2$  and  $\text{CH}_3-\text{CH}_3$ ,
- (b)  $\text{CH}_3-\text{CH}_2\text{OH}$  and  $\text{CH}_3-\text{O}-\text{CH}_3$ ,
- (c)  $\text{CH}_3-\text{CH}_2\text{CN}$  and  $\text{CH}_3-\text{CH}_2-\text{CH}_2\text{NH}_2$ ,
- (d)  $\text{CH}_3-\text{CHOH}-\text{CH}_3$  and  $\text{CH}_3-\text{CH}_2-\text{CHO}$ ,
- (e)  $\text{CH}_3-\text{CH}_2-\text{CHO}$  and  $\text{CH}_3-\text{CO}-\text{CH}_3$ ,
- (f)  $\text{CH}_3-\text{CH}_2-\text{NH}_2$  and  $\text{CH}_3-\text{NH}-\text{CH}_3$ .

83. Show how you could distinguish between the compounds

- (a)  $\text{C}_2\text{H}_5-\text{CO}-\text{NH}_2$  and  $\text{CH}_3-\text{CNOH}-\text{CH}_3$ ,
- (b)  $\text{C}_3\text{H}_7-\text{CO}-\text{OC}_3\text{H}_7$  and  $(\text{C}_3\text{H}_7\text{CO})_2\text{O}$ ,
- (c)  $\text{CH}_3-\text{CHOH}-\text{CO}-\text{OC}_2\text{H}_5$  and  $\text{CH}_3-\text{CH}(\text{OC}_2\text{H}_5)-\text{COOH}$ ,
- (d)  $\text{CH}_3-\text{CO}-\text{CH}_3$  and  $\text{CH}_3-\text{CO}-\text{OCH}_3$ .

84. Write an equation for the equilibrium between acetic acid, ethyl alcohol, water, and ethyl acetate. Write an algebraic equation expressing the equilibrium constant of this reaction. Define each term in the equation.

Predict the effect on the chemical equilibrium (a) of adding concentrated sulfuric acid, (b) of adding potassium hydroxide.

85. Sixty grams of acetic acid with 46 g. of ethyl alcohol gave an equilibrium mixture containing 58.7 g. of ethyl acetate; calculate the equilibrium constant. One mole of acetic acid is mixed with 3 moles of alcohol; calculate the maximum yield of ester (no dehydrating agent present).

86. Write equations for the main reactions which occur when ethyl acetate is mixed with concentrated ammonium hydroxide. Show how the success of this plan for making acetamide is dependent upon differences in the rates of three possible reactions.

87. Write five possible structures for compounds having the formula  $C_4H_8O_2$ . Outline chemical reactions that may be used to identify each compound.

88. Outline two methods for separating ethyl alcohol and acetone without distilling the mixture.

89. Acetone, acetic acid, and methyl alcohol are present in an aqueous solution. How would you separate the components and obtain each in a pure state?

90. Beginning with acetone and any necessary reagents, show how the following compounds may be made: (a)  $(CH_3)_3COH$ , (b)  $(CH_3)_2CCl_2$ , (c)  $(CH_3)_2CHOH$ , (d)  $(CH_3)_2C : CH_2$ .

91. Write two possible structures for compounds having the formula  $C_3H_7NO$ . Outline chemical reactions that may be used to identify each compound.

92. Write all possible structures for a compound having the formula  $C_3H_8O$ . Describe one compound having this formula and outline an experimental procedure that could be used to determine which structure should be assigned to it.

93. Two compounds, each having the formula  $C_3H_8O$ , were oxidized. One of them was converted into  $C_3H_6O$  and the other yielded  $C_3H_6O_2$ . Neither of these products could be further oxidized without loss of carbon. Write the structural formulas of the original compounds.

94. A compound having the formula  $C_2H_2Br_2O$  was converted by cold water into  $C_2H_3BrO_2$ . Write structural formulas for the two compounds.

95. Show how acetic acid, acetic anhydride, and acetamide may be made from acetyl chloride.

96. Indicate by means of balanced equations the action of propionyl bromide (a) on water, (b) on ammonia, (c) on ethyl alcohol, (d) on sodium propionate.

97. Account for the fact that formic acid is the only member of the fatty acid series that acts as a reducing agent.

98. How would you proceed to make an  $\alpha$ -bromo derivative of a saturated monobasic acid? How would you make a  $\beta$ -bromo derivative of the same acid?

99. Show by means of formulas how  $\alpha$ -hydroxy,  $\beta$ -hydroxy, and  $\gamma$ -hydroxy acids behave when heated.



100. Calculate the weight of iodine that will combine with 15 g. of dioleostearin.

101. Two esters have the formula  $C_4H_8O_2$ . Write their structural formulas, and specify the hydrolysis products of each.

102. If a substance were known to be either an alcohol, an aldehyde, or an ester, what tests would you use to identify the class to which it belongs?

103. With the aid of a solution of bromine in carbon tetrachloride, how could you distinguish linoleic acid from oleic acid?

104. Starting with ethyl alcohol and any inorganic compounds, show by means of equations how the acid of the structure  $(C_2H_5)_2CHCOOH$  may be prepared.

105. A compound having the composition  $C_6H_{12}O_2$ , when boiled with a solution of sodium hydroxide, was converted into ethyl alcohol and a compound of the composition  $C_4H_7O_2Na$ . Write the structural formula of the original compound.

106. Write the structural formula of a compound which, on hydrolysis, gives isopropyl alcohol and normal butyric acid.

107. A fat consists of stearin 80 per cent, palmitin 12 per cent, olein 5 per cent, linolein 3 per cent. Calculate its iodine number.

108. An oil contains 4 per cent of linolein. The other components are olein, stearin, and palmitin. Its iodine value is 85. Find the per cent of olein in the oil.

109. Would more or less alkali be required to saponify butter than to saponify an equal weight of beef tallow? Give a reason for your answer.

110. Outline a method by means of which *n*-primary butyl alcohol may be changed into *n*-secondary butyl alcohol.

111. Outline a possible method for the preparation of *n*-propyl alcohol from acetic acid.

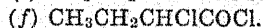
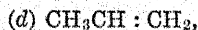
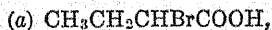
112. Show how bromine may be substituted for the underlined atoms or groups in the following: (a)  $C_2H_5\text{OH}$ , (b)  $(CH_3)_2CO$ , (c)  $CH_3CONH\text{H}$ , (d)  $(CH_3)_4NOH$ .

113. How could ethyl alcohol be made (a) from  $C_2H_5NH_2$ ? (b) from  $C_2H_5CONH_2$ ? (c) from  $C_2H_5I$ ?

114. How could ethylamine be made (a) from  $C_2H_5OH$ ? (b) from  $C_2H_5CONH_2$ ? (c) from  $C_2H_5I$ ?

115. The silver salt of a tribasic acid was decomposed by heat. A sample of salt weighing 0.511 g. left a residue of silver weighing 0.322 g. Calculate the molecular weight of the acid.

116. Write equations showing how  $CH_3CH_2CH_2COOH$  may be transformed into



117. Devise methods for making the following compounds from ethyl alcohol: (a)  $CH_3COOH$ , (b)  $CH_3CH_2Cl$ , (c)  $(CH_3CO)_2O$ , (d)  $CH_2=CH_2$ , (e)  $CH_2BrCH_2Br$ .

118. Write equations for reactions by which substances having the following formulas may be prepared: (a)  $\text{CH}_3(\text{C}_2\text{H}_5)_2\text{N}$ , (b)  $(\text{CH}_3)_2\text{NH}$ , (c)  $\text{CH}_3\text{CON}(\text{C}_2\text{H}_5)_2$ .

119. How would you distinguish a water solution of acetamide from a water solution of methylamine?

120. Describe, with the aid of equations, a method for converting ethyl alcohol into *n*-butyl alcohol.

121. Write the structural formulas for all monocarboxylic unsaturated acids having four carbon atoms.

122. Write equations for reactions by which propionic aldehyde,  $\text{C}_2\text{H}_5\text{CHO}$ , can be converted into (a) propionic acid, (b) secondary butyl alcohol, (c) diethyl ketone.

123. Write graphic formulas of all acids that can be formed by the oxidation of propylene glycol,  $\text{CH}_3 \cdot \text{CHOH} \cdot \text{CH}_2\text{OH}$ .

124. Write two balanced equations for reactions by which isobutyric acid may be prepared from isobutyl alcohol.

125. Outline methods for making (a)  $\alpha$ -iodopropionic acid, (b)  $\beta$ -iodopropionic acid.

126. Contrast the behavior of aqueous sodium hydroxide on the following compounds:  $\text{CH}_2\text{I} \cdot \text{CH}_2 \cdot \text{COOH}$  and  $\text{CH}_3 \cdot \text{CHI} \cdot \text{COOH}$ .

127. Write the structural formulas of the acids having the empirical formula  $\text{C}_5\text{H}_{11}\text{COOH}$ . Name each acid.

128. How could you distinguish an olein soap from one made from stearin?

129. What volume of oxygen (calculated at 760 mm. pressure and  $30^\circ \text{C}$ .) is taken from the air in the conversion of 1000 g. of alcohol into acetic acid?

130. Outline methods for making (a) formic acid from oxalic acid, (b) oxalic acid from formic acid, (c) acetic acid from malonic acid, (d) malonic acid from acetic acid.

131. An excess of ammonium oxalate was added to 50 cc. of a calcium chloride solution. The precipitated calcium oxalate was dissolved in sulfuric acid and titrated with potassium permanganate (3 g. of  $\text{KMnO}_4$  per liter). If 35 cc. of the permanganate solution was used, calculate the normality of the  $\text{CaCl}_2$  solution.

132. Assuming that nitrogen, carbon dioxide, and water are the products of explosion of nitroglycerine, and that the excess oxygen, if any, remains in the form of oxygen gas, how many gram-molecules of gas would be formed from one gram-molecule of nitroglycerine?

133. How many cubic centimeters of normal alkali solution will be neutralized by 2 g. of anhydrous oxalic acid?

134. Two compounds having the formula  $\text{C}_2\text{H}_4\text{Cl}_2$  are known. Write their structural formulas, and show how they may be made.

135. Write balanced equations representing the action of the following reagents upon ethyl alcohol: (a)  $\text{H}_2\text{SO}_4$ , (b)  $\text{CH}_3\text{COOH}$ , (c)  $\text{PCl}_3$ , (d)  $\text{K}_2\text{Cr}_2\text{O}_7 + \text{H}_2\text{SO}_4$ .

136. Show how fumaric acid may be converted into (a) succinic acid, (b) monobromosuccinic acid, (c) dibromosuccinic acid, (d) tartaric acid.

137. Write three possible structures for compounds having the formula  $C_4H_7OCl$ . Outline chemical reactions that may be used to identify each compound.

138. One gram of glucose, when added to an excess of Fehling's solution and heated on a water bath, precipitated 1.2 g. of cuprous oxide. Compare this value with that calculated, assuming the glucose to be oxidized to gluconic acid.

139. Write an equation for the esterification of butyric acid by ethyl alcohol. Write an algebraic expression for the equilibrium constant of the reaction. A mixture consisting of 0.3 mole of pure ethyl alcohol and 0.1 mole of pure butyric acid was allowed to stand until equilibrium was established. The mixture was then titrated with a base so rapidly that no ethyl butyrate was hydrolyzed. To neutralize the solution 150 cc. of half-normal alkali was required. Find the value of the equilibrium constant.

140. With the aid of any necessary inorganic reagents, show by equations how it would be possible to prepare (a) ethyl acetate from alcohol, (b) acetyl chloride from ethyl acetate, (c) formaldehyde from methyl alcohol.

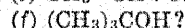
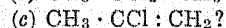
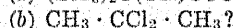
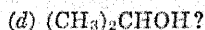
141. The ionization constant of acetic acid is  $1.82 \times 10^{-5}$ . Calculate the pH of a 0.2 N solution of the acid.

142. The pH of a 0.1 N solution of a certain acid is 3.1. Find the concentration of hydrogen ions (moles of  $H^+$  per liter of solution) in the 0.1 N solution.

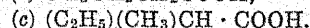
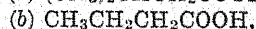
143. The dissociation constant of propionic acid is  $1.34 \times 10^{-5}$ . Calculate the pH of a 0.15 N solution of the acid.

144. The dissociation constant of acetic acid is  $1.82 \times 10^{-5}$ . Calculate the per cent of acetic acid ionized in a 0.3 N solution.

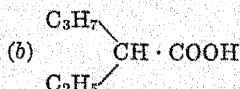
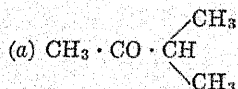
145. From acetone how would you prepare



146. Write equations indicating the use of malonic ester in preparing



147. Write equations showing how the following compounds may be obtained by means of the acetoacetic ester synthesis:



148. Write equations representing the preparation of isobutyric acid by the malonic ester synthesis and by the acetoacetic ester synthesis.

149. Starting with 50 g. of malonic ester and going to diethylacetic acid, calculate the amounts of the reagents required in each step. Assume an 80 per cent yield in each reaction.

150. Would the monoacetyl derivative of mesotartaric acid be optically active?

151. Assuming that Fehling's solution oxidizes glucose to gluconic acid, what weight of cuprous oxide would be precipitated by the action of Fehling's solution on 5 g. of glucose?

152. Calculate the amount of acetic anhydride necessary to completely acetylate 1 g. of glucose,  $C_6H_{12}O_6 \cdot H_2O$ .

153. Assume that there are only two forms of glucose, one with a specific rotation of  $110^\circ$  and the other with a specific rotation of  $19^\circ$ . The equilibrium mixture has a specific rotation of  $52.7^\circ$ . In what proportions are two components present in the equilibrium mixture?

154. What volume of carbon dioxide measured at  $30^\circ$  and 750 mm. may be obtained from 10 g. of glucose by fermentation?

155. Write equations for (a) the fermentation of glucose, (b) the action of phenylhydrazine on glucose, (c) the oxidation of glucose by Fehling's solution.

156. What volume of nitrogen measured at  $30^\circ$  and 740 mm. will be obtained when an excess of alkaline sodium hypobromite acts upon 3 g. of urea?

157. What volume of nitrogen at  $18^\circ$  and 740 mm. will be obtained from 1.4 g. of amylamine and an excess of nitrous acid?

158. Is phosgene an acid chloride? How does it react with water, with ammonia, and with alcohol?

159. One gram of a pure monoamino acid, upon treatment with nitrous acid, yields 254 cc. of nitrogen, measured at standard conditions. What is the molecular weight of the acid?

160. Write the formulas of the possible tetrapeptides obtainable from glycine, valine, leucine, and tyrosine.

161. What volume of nitrogen at  $20^\circ$  and 760 mm. is liberated when an excess of nitrous acid acts upon 1.2 g. of urea? What volume of carbon dioxide is formed in the same reaction? How are the two gases separated? How are they estimated quantitatively?

162. What is the mole fraction of water in a solution containing equal weights of alcohol and water?

163. A liquid is known to be a hydrocarbon. Give qualitative tests that will determine whether it is a paraffin, an unsaturated aliphatic hydrocarbon, or an aromatic compound.

164. Write structural formulas for all compounds having the empirical formula  $C_8H_{10}$ . Devise experimental methods for distinguishing and identifying them.

165. Outline a method for preparing each of four compounds having the formula  $C_7H_7Cl$ .

166. Devise methods for making the following compounds from benzene: (a) *metadichlorobenzene*, (b) *orthonitrophenol*, (c) *paratoluidine*.

167. Two compounds have the formula  $C_8H_{10}$ . One of them yields two mononitro derivatives, the other only one. On oxidation each yields an acid which has the formula  $C_8H_6O_4$ . Write structural formulas for the two hydrocarbons.

168. Indicate the action of nitrous acid on ethylamine,  $C_2H_5NH_2$ , and on aniline,  $C_6H_5NH_2$ , in hot and in cold solutions.

169. What tests may be used to distinguish between primary, secondary, and tertiary amines? primary, secondary, and tertiary alcohols? alcohols and phenols? aliphatic and aromatic amines?

170. What volume of nitrogen gas measured at standard conditions would be evolved by treatment of 1 g. of aniline with an excess of nitrous acid?

171. Write the formulas of the chief products formed in the sulfonation of iodobenzene, methyl benzene, and nitrobenzene.

172. The heat of combustion of benzene is 9977 calories per gram. Determine whether benzene is an endothermic or an exothermic compound.

173. What weight of tin is necessary to reduce 50 g. of nitrobenzene? Assume that the tin is converted into stannous ions.

174. Write the formula of the amide which would be used in the preparation of benzylamine. Write a balanced equation representing the conversion of the amide to the amine.

175. Prepare a chart of the oxidation products of aniline and the reduction products of nitrobenzene. Specify the reagents used in making each of these products.

176. Write equations representing a method for replacing a hydrogen atom in benzene by each of the following: (a) OH, (b)  $NH_2$ , (c) COOH, (d)  $NO_2$ , (e) Br, (f)  $C_2H_5$ .

177. Write equations representing the reactions between phenol and the following reagents: (a) KOH, (b)  $HNO_3$ , (c)  $Br_2$ , (d)  $CH_3COCl$ .

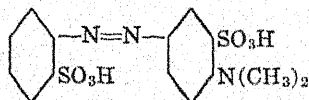
178. Calculate the quantities of hydrochloric acid and sodium nitrite required to convert 60 g. of aniline into phenol. What volume of nitrogen measured at  $30^\circ$  and 750 mm. will be evolved in the process?

179. Explain the fact that phenol precipitates when a solution of sodium phenolate is saturated with carbon dioxide.

180. Phenol has acidic properties and sodium phenolate is not volatile, but to prevent the steam distillation of phenol from aqueous solution a large excess of NaOH is necessary. Explain.

181. Beginning with benzene, outline a method for synthesizing the dye dimethylaminoazobenzene,  $C_6H_5N_2C_6H_4N(CH_3)_2$ .

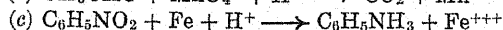
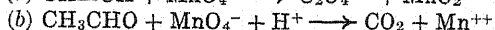
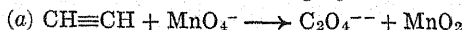
182. Beginning with o-aminobenzenesulfonic acid, methyl iodide, and any necessary inorganic reagents, outline a method for the preparation of a dye having the formula



183. Outline qualitative chemical tests to distinguish the following pairs of compounds (one test for each pair); the tests must not be based upon boiling points, freezing points, colors, or odors:

- |                                     |                                     |
|-------------------------------------|-------------------------------------|
| (a) Phenol and aniline.             | (c) Butyraldehyde and acetophenone. |
| (b) Ethyl iodide and ethyl alcohol. | (d) Fluorescein and methyl orange.  |
| (e) Starch and cellulose.           |                                     |

184. Complete and balance the following equations:



185. How would you obtain phenol from a mixture of phenol and hydrocarbons when the boiling points are such that they cannot be separated by fractional distillation?

186. Devise methods for making the following compounds from benzene:

(a) *metadibromobenzene*, (b) *orthonitrophenol*, (c) *paraxylene*.

187. Show by means of equations how the following compounds may be converted into benzene: (a)  $\text{CH}_3\text{C}_6\text{H}_5$ , (b)  $\text{C}_6\text{H}_5\text{COOH}$ , (c)  $\text{C}_6\text{H}_5\text{NH}_2$ , (d)  $\text{C}_6\text{H}_5\text{CONH}_2$ , (e)  $\text{C}_6\text{H}_5\text{NO}_2$ .

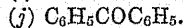
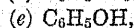
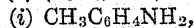
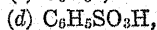
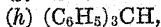
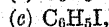
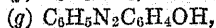
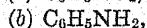
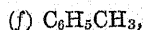
188. How may toluene be converted into benzyl chloride? into benzyl alcohol? into benzoic acid? into benzene?

189. Three different dichlorobenzoic acids, when heated with soda lime, yield the same dichlorobenzene. Write the structural formulas of the three acids.

190. Show by means of equations the steps involved in making benzoic acid (a) from toluene, (b) from benzaldehyde, (c) from benzonitrile.

191. Make plans for separating mixtures of (a) phenol and aniline, (b) phenol and benzene, (c) aniline and nitrobenzene, (d) phenol and benzoic acid.

192. Beginning with benzene and any necessary reagents, show by balanced equations how the following compounds may be made:



193. Indicate by equations, or in words, a method of obtaining (a) a ketone from a secondary alcohol, (b) an acid chloride from an acid, (c) a phenol from a primary aromatic amine, (d) a monosaccharide from a disaccharide.

194. Tabulate the molecular structures that are susceptible to hydrolysis. Name compounds representing specific examples of these structural types. Indicate by names and formulas the hydrolysis products of the compounds used as specific examples.

195. A compound has the following composition:

|                    |        |
|--------------------|--------|
| Carbon . . . . .   | 40.0 % |
| Hydrogen . . . . . | 6.6 %  |
| Oxygen . . . . .   | 53.3 % |

Its molecular weight is 90. It reduces Fehling's solution and with phenylhydrazine forms an osazone. It reacts with one molecule only of hydrogen cyanide, forming a cyanhydrin. With acetyl chloride it yields a compound having the formula  $\text{C}_7\text{H}_{10}\text{O}_5$ . It can be oxidized by dichromate ion to a monobasic acid,  $\text{C}_3\text{H}_5\text{O}_4$ , and by nitric acid to a dibasic acid,  $\text{C}_3\text{H}_4\text{O}_5$ .

Write the structural formula of the compound and write balanced equations representing its action upon the reagents mentioned.

196. Write equations representing a method for replacing a hydrogen atom in benzene by each of the following: (a) CN, (b) Cl, (c) COOH, (d) CH<sub>3</sub>, (e) N<sub>2</sub>C<sub>6</sub>H<sub>5</sub>.

197. Show how the diazo reaction may be used to convert aniline into each of the following compounds:

- |                                       |   |
|---------------------------------------|---|
| (a) C <sub>6</sub> H <sub>5</sub> OH, | (c) C <sub>6</sub> H <sub>5</sub> COOH,                                       |
| (b) C <sub>6</sub> H <sub>5</sub> Br, | (d) C <sub>6</sub> H <sub>5</sub> · N : N · C <sub>6</sub> H <sub>4</sub> OH. |

198. Write equations for reactions by which the following may be prepared by means of the Friedel and Crafts reaction:

- |   |   |
|---|---|
| (a) CH <sub>3</sub> · C <sub>6</sub> H <sub>4</sub> · C <sub>2</sub> H <sub>5</sub> , | (c) CH <sub>3</sub> CO · C <sub>6</sub> H <sub>4</sub> · CH <sub>3</sub> ,          |
| (b) C <sub>6</sub> H <sub>5</sub> CHO,  | (d) CH <sub>2</sub> (C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> ) <sub>2</sub> . |

199. Write the structural formulas of the compounds formed by the introduction of one and of two nitro groups into (a) C<sub>6</sub>H<sub>5</sub>C<sub>2</sub>H<sub>5</sub>, (b) C<sub>6</sub>H<sub>5</sub>OH, (c) C<sub>6</sub>H<sub>5</sub>Br, (d) C<sub>6</sub>H<sub>5</sub>NO<sub>2</sub>, (e) C<sub>6</sub>H<sub>5</sub>COOH.

200. Starting with benzene, write equations for reactions by which the following compounds may be made: (a) C<sub>6</sub>H<sub>4</sub>ClNO<sub>2</sub> (*meta*), (b) C<sub>6</sub>H<sub>4</sub>ClNO<sub>2</sub> (*para*), (c) C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>I (*meta*).

201. Indicate the action of the Grignard reagent upon (a) a ketone, (b) an ester, (c) an amine, (d) an alcohol.

202. Write balanced equations for all operations involved in making propionic acid by means of either the malonic ester synthesis or the Grignard reaction.

203. Show how the Friedel and Crafts reaction may be used in the preparation of (a) C<sub>6</sub>H<sub>5</sub> · CO · CH<sub>3</sub>, (b) CH<sub>3</sub> · C<sub>6</sub>H<sub>4</sub> · C<sub>2</sub>H<sub>5</sub>, (c) (C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>CH.

204. Write equations for reactions by which C<sub>2</sub>H<sub>5</sub>CHO may be converted into (a) C<sub>2</sub>H<sub>5</sub> · CHO · C<sub>2</sub>H<sub>5</sub>, (b) C<sub>2</sub>H<sub>5</sub> · CO · C<sub>2</sub>H<sub>5</sub>, (c) C<sub>2</sub>H<sub>5</sub>COOH.

205. Write the formulas of the possible products of the action of nitric acid on (a) *orthodichlorobenzene*, (b) *parachlorotoluene*, (c) *metadinitrobenzene*.

206. How would you prepare (a) *metanitrochlorobenzene*? (b) *ethylbenzene*? (c) *benzonitrile*?

207. Naphthionic acid is diazotized and coupled with dimethylaniline. Write the formula of the product.

208. How would you prepare diphenylethyl carbinol?

209. Outline a synthesis of (a) *paranitrobenzaldehyde*, (b) *metabromobenzaldehyde*, (c) *tolyphenyl ketone*.

210. Phenylhydrazine is made to react with an unknown compound. The hydrazone formed has a molecular weight of 176. What is the molecular weight of the unknown compound?

211. Write the formulas of the products formed when hydrocyanic acid, sodium bisulfite, and phenylhydrazine react with benzaldehyde. Would any of these products exist in *syn* and *anti* forms?

212. Write structural formulas for six trihydroxybenzoic acids.



213. Show by equations how the following substances may be prepared by the use of diazo compounds: (a)  $\text{HOC}_6\text{H}_4\text{C}_2\text{H}_5$  (*para*), (b)  $\text{ClC}_6\text{H}_4\text{COOH}$  (*para*), (c)  $\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$  (*para*).

214. Write equations for reactions by which aromatic acids may be prepared by means of (a) the oxidation of a hydrocarbon, (b) the hydrolysis of a nitrile, (c) malonic ester synthesis, (d) acetoacetic ester synthesis.

215. Indicate by means of structural formulas the reactions of triphenylmethane dyes with acids and with bases.

216. Outline a method for preparing (a) an azo dye, (b) a triphenylmethane dye.

217. The following neutral substances are each heated with dilute sodium hydroxide under a reflux condenser and the resulting solution subjected to steam distillation. What product would you expect to find (1) in the distillate, (2) remaining in the distilling flask, — (a) ethyl acetate, (b) acetanilide, (c) methyl acetoacetate, (d) phenyl acetate, (e) valeric anhydride?

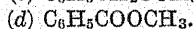
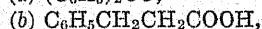
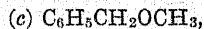
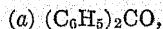
218. Show how malonic ester may be used in the synthesis of amino acids.

219. Use Thiele's theory of partial valence to explain why bromine attaches to the  $\beta$ -carbon atom when an  $\alpha$ - $\beta$ -unsaturated acid is treated with hydrogen bromide.

220. Show how the Grignard reaction may be used in the synthesis of (a) acids, (b) primary alcohols, (c) tertiary alcohols.

221. Outline methods for preparing the following compounds from acetone: (a)  $\text{CH}_3\text{—C}\equiv\text{CH}$ , (b)  $(\text{CH}_3)_2\text{C}(\text{OH})\text{C}_6\text{H}_7$ , (c)  $(\text{CH}_3)_2\text{C}(\text{OH})\text{COOH}$ .

222. Beginning with  $\text{C}_6\text{H}_5\text{CHO}$  and any necessary reagents, show how the following compounds may be made:



223. A compound of the composition  $\text{C}_8\text{H}_9\text{Br}$  was converted by oxidation into *parabromobenzoic acid*. Write the graphic formula of the compound.

224. How many monosubstitution products of isoquinoline are possible? How many disubstitution products are possible if the substituents are alike?

225. An alkaloid with one atom of nitrogen in the molecule forms a crystalline sulfate containing one molecule of water of crystallization. Two grams of the sulfate on treatment with barium chloride yields 0.875 g. of barium sulfate. What is the molecular weight of the alkaloid?

226. Give two examples of intramolecular rearrangement involving the shift of an atom or group from nitrogen to carbon. State how the transformation is induced in each case.

227. Define and illustrate (a) the Cannizzaro reaction, (b) benzoin condensation, (c) the Perkin synthesis, (d) the Friedel and Crafts reaction, (e) aldol condensation.

228. Outline an experimental procedure for separating and purifying the components of the following mixtures; do not resort to fractional distillation: (a) phenol and aniline, (b) ethyl iodide and ethyl alcohol, (c) benzaldehyde and benzyl alcohol.



229. Which of the following reactions proceeds at the fastest rate?

- (a)  $\text{CH}_3\text{COOC}_2\text{H}_5 + \text{H}_2\text{O} + \text{NH}_3 \longrightarrow \text{CH}_3\text{COONH}_4 + \text{C}_2\text{H}_5\text{OH}$ .  
 (b)  $\text{CH}_3\text{COOC}_2\text{H}_5 + \text{H}_2\text{O} + \text{NH}_3 \longrightarrow \text{CH}_3\text{CONH}_2 + \text{C}_2\text{H}_5\text{OH} + \text{H}_2\text{O}$ .  
 (c)  $\text{CH}_3\text{CONH}_2 + \text{H}_2\text{O} \longrightarrow \text{CH}_3\text{COONH}_4$ .

Support your conclusion by experimental evidence. If you are not familiar with the facts, outline, in detail, an experiment that could be made to determine the relative rates of these reactions.

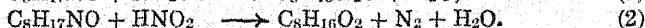
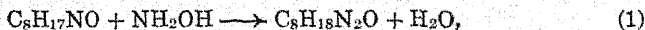
230. Complete the following equations. Write the names and structures of the main products. (In each case an excess of the second reagent is used.)

- (a) Acetyl chloride + aniline  $\longrightarrow$   
 (b) Ethyl iodide + silver acetate  $\longrightarrow$   
 (c) Ethyl iodide + dimethylamine  $\longrightarrow$   
 (d) Acetone + sodium bisulfite  $\longrightarrow$   
 (e) Acetaldehyde + hydrogen cyanide  $\longrightarrow$   
 (f) Benzaldehyde + potassium cyanide  $\longrightarrow$   
 (g) Benzaldehyde + concentrated sodium hydroxide  $\longrightarrow$   
 (h) Phenol + bromine  $\longrightarrow$   
 (i) Glucose + phenylhydrazine  $\longrightarrow$   
 (j) Methylacetylene + silver ammonia ion  $\longrightarrow$   
 (k) Ethyl iodide + triethylamine  $\longrightarrow$   
 (l) Benzoyl chloride + aniline  $\longrightarrow$

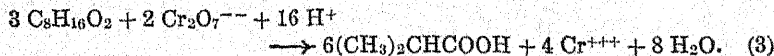
231. A compound has the formula  $\text{C}_4\text{H}_8\text{O}_4$ . With acetyl chloride it yields a derivative corresponding to the formula  $\text{C}_{10}\text{H}_{14}\text{O}_7$ . With hydroxylamine it forms an oxime,  $\text{C}_4\text{H}_8\text{NO}_4$ . The compound can be oxidized to a dibasic acid having the formula  $\text{C}_4\text{H}_6\text{O}_6$ . It can be reduced to a compound,  $\text{C}_4\text{H}_{10}\text{O}_4$ , which is optically inactive and cannot be resolved into optically active components. This reduction product fails to form an oxime, but it reacts with acetic anhydride, forming an acetyl derivative,  $\text{C}_{12}\text{H}_{18}\text{O}_8$ . Write the structural formula of the compound.

232. A compound, A, having the empirical formula  $\text{C}_8\text{H}_{15}\text{NO}_4$ , reacts with  $\text{HNO}_2$ , yielding free nitrogen and a product having the formula  $\text{C}_8\text{H}_{14}\text{O}_5$ . When heated with an aqueous solution of  $\text{KOH}$  the original compound yields ethyl alcohol and a salt corresponding to the formula  $\text{C}_4\text{H}_5\text{NO}_4\text{K}_2$ . Write a structural formula for the compound A.

233. A compound having the formula  $\text{C}_8\text{H}_{17}\text{NO}$  reacts with hydroxylamine and with nitrous acid as follows:



The compound  $\text{C}_8\text{H}_{16}\text{O}_2$ , formed in reaction (2), can be oxidized to isobutyric acid as indicated in (3).



Write a structural formula for the compound  $\text{C}_8\text{H}_{17}\text{NO}$  and indicate clearly what each reaction contributes to the establishment of the structure of the molecule.

# INDEX

(Principal references in black type)

- Abderhalden, Emil, 304  
Acetaldehyde, 78  
Acetals, 75, 154  
Acetanilide, 217  
Acetic acid, 82, 88, 109  
Acetoacetic ester, 420  
Acetone, 68, 80  
Acetonitrile, 148  
Acetophenone, 245  
Acetylacetone, 289  
Acetylene, 81  
Acetylene tetrachloride, 60  
Acetylsalicylic acid, 251  
Acid anhydrides, 96, 126  
Acid chlorides, 94  
Acids, aliphatic monobasic, 81, 109;  
    aliphatic polybasic, 121; aliphatic  
    unsaturated, 93, 130; aromatic di-  
    basic, 252; aromatic monobasic,  
    247; aromatic unsaturated, 251  
Acrolein, 79  
Acrylic acid, 93  
Acyl radicals, 84  
Adair, G. S., 292  
Adams, Roger, 119, 232  
Adenase, 184  
Adenine, 321, 322  
Adipic acid, 121  
Adrenaline, 222  
Alanine, 293, 294, 300, 306  
Alanylglycine, 300  
Alanyltirosine, 303  
Albertson, J. N., 101  
Albumin, 292, 307  
Albuminoids, 307  
Alcohols, aliphatic monohydric, 39;  
    aliphatic polyhydric, 47; aliphatic  
    unsaturated, 50; aromatic, 242  
Aldehydes, aliphatic, 66; aromatic,  
    242  
Aldol condensation, 71, 413  
Alizarin, 284, 285  
Alizarin dyes, 283  
Alkaloids, 326  
Alkyl halides, 52, 56  
Alkyl radicals, 12  
Allan, J., 261  
Allen, Paul, 417  
Allyl alcohol, 50  
Alphen, J. van, 449  
Amides, 107, 127  
Amines, aliphatic, 136, 373; aro-  
    matic, 216, 373  
Amino acids, 110, 293, 306  
Aminoacetic acid, 82, 294  
Aminoazobenzene, 272  
Aminoglutaric acid, 297  
Aminoisobutylacetic acid, 295  
Aminoisovaleric acid, 295  
Aminopropionic acid, 294  
Aminosuccinic acid, 297  
Ammonia system, 143  
Amygdalin, 244  
Amyl alcohol, 45, 46  
Amyl bromide, 56  
Amyl chloride, 56  
Amyl iodide, 56  
Amylamine, 143  
Amylene, 21  
Amylopsin, 184  
Analytical methods, 1  
Aniline, 212, 217  
Anisol, 241  
Anthracene, 201, 202, 283  
Anthrahydroquinoneazine, 285  
Anthranilic acid, 248, 286  
Anthraquinol, 284  
Anthraquinone, 202, 283  
Arabinose, 165, 167  
Arabitol, 49  
Arginine, 293, 297  
Armstrong, Henry E., 190  
Aryl halides, 204  
Aryl radicals, 192  
Aspartic acid, 293, 297, 306  
Asphalt, 20  
Aspirin, 251  
Asymmetric syntheses, 118

- Atropic acid, 336  
Atropine, 336, 339  
Aurine, 280  
Auxochrome, 289  
Ayers, Eugene E., 45  
Azelaic acid, 121  
Azo dyes, 271  
Azobenzene, 211  
Azoxybenzene, 211, 214
- Bachman, W. E., 266  
Baeyer, Adolph, 190, 414  
Baker, J. W., 443  
Baking powders, 132  
Barger, George, 293  
Bateman, Dorothy, 447  
Beckmann, Ernst, 378, 437  
Beckmann rearrangement, 437  
Bennett, G. M., 442  
Benzal chloride, 204  
Benzalaniline, 216  
Benzaldehyde, 242, 244, 276  
Benzaldoxime, 244  
Benzamide, 248  
Benzene, 36, 185; constitution of, 186; homologues of, 192  
Benzenediazo hydroxide, 225, 272  
Benzenediazonium hydroxide, 225  
Benzenesulfonic acid, 206, 231  
Benzenesulfonyl chloride, 206  
Benzenetrisulfonic acid, 206  
Benzhydrol, 246  
Benzhydryltetraphenylmethane, 268  
Benzidine, 215; diazo derivative of, 274  
Benzil, 289, 445  
Benzoazurine, 274  
Benzoic acid, 208, 247, 263  
Benzoic sulfimide, 250  
Benzoin, 446  
Benzoin condensation, 414  
Benzophenone, 197, 245, 246  
Benzophenone chloride, 197  
Benzotrichloride, 204  
Benzoyl chloride, 247  
Benzoylacetophenone, 289  
Benzoyltropine, 341  
Benzpinacol, 246  
Benzyl alcohol, 231, 242  
Benzyl bromide, 205  
Benzyl chloride, 204  
Bernard, Hans, 270  
Biddle, H. C., 344  
Bidiphenylene-ethylene, 289  
Biot, J. B., 114  
*Bis*-lead triphenyl, 270  
Biuret reaction, 308  
Bogert, M. T., 397  
Borgstrom, Parry, 270  
Bosworth, A. W., 309  
Braconnot, H., 292  
Branch, G. E. K., 269  
Brickner, W., 446  
Britton, Edgar C., 232  
Bromoacetic acid, 82  
Bromobenzene, 205, 261  
Bromoform, 58  
Bromotoluene, 205  
Brooks, Benj. T., 94  
Burr, G. O., 314  
Butane, 10, 16  
Butyl alcohol, 44, 46  
Butyl nitrate, 105  
Butyl nitrite, 105  
Butylamine, 143  
Butylene, 21  
Butyric acid, 82, 91, 109  
Butyrolactone, 112  
Butyronitrile, 148
- Caffeine, 321, 322  
Calcium cyanamide, 146  
Calvert, H. T., 372  
Camphane, 359  
Camphor, 360, 362  
Camphoric acid, 362  
Camphoronic acid, 362  
Cane sugar, 174, 176; hydrolysis of, 365  
Cannizzaro reaction, 244, 415  
Caproic acid, 82, 109  
Caprylic acid, 109  
Carane, 359  
Carbazole, 201  
Carbohydrates, 151  
Carbolic acid, 231  
Carbon tetrachloride, 11, 59  
Carotene, 311  
Carvacrol, 235, 358  
Carvone, 358  
Casein, 309  
Catechol, 221, 236  
Cathcart, L. P., 305  
Cellobiose, 178  
Cellosolves, 65  
Cellulose, 181  
Chapin, W. H., 462  
Chapman, A. W., 442

- Chapman, L. M., 301  
Chattaway, F. D., 450  
Chloroacetic acid, 82  
Chloroacetyl catechol, 221  
Chlorobenzene, 204, 205  
Chloroform, 11, 57, 60  
Chlorophenol, 236  
Chloropierin, 59  
Chloroprene, 30  
Chloropropionyl chloride, 303  
Chlorotoluene, 204  
Cholesterol, 314  
Choline, 104  
Chrom violet, 280  
Chromophore groups, 288  
Chrysaniline, 279  
Ciba violet, 287  
Cinchonine, 344  
Cinchotoxine, 345  
Cineol, 354  
Cinnamaldehyde, 364  
Cinnamic acid, 251, 405  
Citral, 351  
Citric acid, 135  
Citronellal, 350  
Claisen, L., 414, 421  
Clark, W. M., 82  
Claus, A., 191  
Clough, George W., 455  
Coal tar, 185, 231, 234  
Cocaine, 339, 341  
Cohen, J. B., 372  
Cohn, Edwin J., 301  
Conant, James B., 269  
Condensation processes, 395  
Cone, L. H., 412  
Congo red, 274  
Coniine, 332  
Conjugated systems, 386  
Conjugation and resonance, 385  
Conner, R. B., 59  
Conyryne, 333  
Corson, B. B., 417  
Coumarin, 364  
Coyne, F. P., 293  
Crafts, J., 406  
Creosote, 234  
Cresol, 231, 234, 254  
Crotonaldehyde, 80  
Crotonic acid, 111  
Crum-Brown and Gibson rule, 258  
Crystal violet, 276, 277  
Cumene, 194  
Curtius, Th., 436  
Curtius rearrangement, 436  
Cyamelide, 150  
Cyanamide, 146  
Cyanates, 145, 149  
Cyanhydrin synthesis, 161  
Cyanic acid, 149  
Cyanides, 145, 148  
Cyanoacetic acid, 82  
Cyanogen, 145  
Cyanuric acid, 149  
Cyclobutane, 36  
Cycloheptane, 36  
Cyclohexane, 35, 36  
Cyclooctane, 36  
Cycloparaffins, 36  
Cyclopentane, 35, 36  
Cyclopropane, 36  
Cymene, 194, 195, 234, 351  
Cymene sulfonic acid, 235  
Cystine, 293, 296  
Dalton, John, 4  
Danilow, S., 442  
Darapsky, A., 436  
Decane, 10  
Decylene, 21  
Dehn, W. M., 59  
Dextrose, 172  
Diacetyl, 289  
Diaminocaproic acid, 297  
Diazo compounds, 271  
Diazo reaction, 224  
Diazoaminobenzene, 272  
Diazonium compounds, 225, 232, 271  
Dibenzoyl ethylene, 289  
Dibiphenylenediphenylethane, 268  
Dibromobenzene, 205  
Dibromo-*metaxylylene*, 205  
Dibromopropane, 35  
Dibromoxylene, 205  
Dibutyl ether, 64  
Dicarboxylic acids, 252  
Dichloroacetic acid, 82  
Dichloroadenine, 323  
Dichlorobenzene, 204  
Dichloroethyl sulfide, 22  
Dichlorohypoxanthine, 323  
Dichloropropane, 60  
Dichlorotoluene, 204  
Diethyl ether, 62  
Diethylacetone nitrile, 148  
Dihydric phenols, 236  
Diisoamyl ether, 64  
Diisobutyl ether, 64

- Diisopropyl ether, 64  
Diketopiperazines, 302  
Dimethyl ether, 64  
Dimethylaminoazobenzenesulfonic acid, 273  
Dimethylaniline, 222, 276  
Dimethylethylene, 21  
Dinitrobenzene, 209  
Dioleostearin, 101  
Dioxane, 65  
Dipentene, 356, 360  
Diphenic acid, 196, 203  
Diphenyl, 195  
Diphenyl ether, 241  
Diphenylamine, 221  
Diphenylcarbinol, 242  
Diphenylenediphenylethylene, 288  
Diphenylfulvene, 288  
Diphenylmethane, 196  
Dipropargyl, 187  
Dipropyl ether, 64  
Disaccharides, 174  
Dissociation constants of acids, 82, 252  
Dodecane, 10  
Drewsen, Viggo, 414  
Dulcitol, 49  
Dyes, 271; acridine, 279; alizarin, 283; azo, 271; indigoid, 286; phthaleins, 281; triphenylmethane, 275  
Dynamite, 106  
  
Ecgonine, 340  
Edestin, 297  
Eicosane, 10  
Electrolysis of salts, 411  
Emulsin, 184  
Enzymes, 182  
Eosine, 283  
Ephedrine, 222  
Erepsin, 184  
Ergosterol, 313, 314  
Erythritol, 49  
Essential oils, 349  
Esters, 97  
Ethane, 10  
Ethers, 62  
Ethyl acetate, 99  
Ethyl alcohol, 43, 46  
Ethyl bromide, 56  
Ethyl chloride, 56, 57  
Ethyl ether, 64  
Ethyl iodide, 56  
Ethyl nitrate, 105  
Ethyl nitrite, 105  
Ethyl sulfuric acid, 23, 28, 62  
Ethylamine, 143  
Ethylbenzene, 194  
Ethylbutyl ether, 64  
Ethylene, 21, 26  
Ethylene bromide, 59  
Ethylene chlorhydrin, 48  
Ethylene chloride, 48, 59  
Ethylene dichloride, 26, 60  
Ethylene glycol, 47  
Ethylene hydrocarbons, 21  
Ethylene iodide, 60  
Ethylidene chloride, 60  
Ethylpropyl ether, 64  
Eugenol, 363  
Evans, H. M., 314  
Evans, Mildred W., 269  
Evans, P. N., 101  
  
Fahraeus, Robin, 292  
Fats, 101  
Fehling's solution, 73, 157  
Fischer, Emil, 171, 195, 418, 456  
Fittig, R., 416  
Fittig's synthesis, 193  
Fluoran, 282  
Fluorene, 196  
Fluorescein, 282  
Fluorobenzene, 228  
Flürscheim, B., 258  
Fodor, Andor, 304  
Formaldehyde, 76  
Formic acid, 82, 85  
Formyl chloride, 95, 244  
Frankfurter, Fritz, 270  
Frankland, E., 4, 405  
Franklin, E. C., 144  
Free radicals, 266  
Friedel and Crafts reaction, 193, 196, 201, 406  
Fulminates, 149  
Fulminic acid, 150  
Fulvene, 288  
Fumaric acid, 130  
Furan, 155  
  
Gabriel, S., 418  
Gabriel's synthesis, 253, 418  
Galactose, 169, 174  
Gallic acid, 239  
Gambarjan, S., 269  
Gasoline, 20

- Gattermann, Ludwig, 412, 446  
Gattermann's reaction, 244  
Geneva system, 18  
Geometrical isomers, 24, 226, 244  
Geraniol, 351  
Gilman, H., 395  
Glattfeld, J. W. E., 161  
Gliadin, 297  
Globulins, 307  
Glucose, 155  
Glutamic acid, 293, 297, 306  
Glutaric acid, 121  
Glutelins, 307  
Glycerol (glycerine), 48  
Glycine, 293, 294, 300, 306  
Glycogen, 181  
Glycogenase, 184  
Glycoproteins, 307  
Glyoxylic acid, 47, 308  
Goldschmidt, Stefan, 270  
Gomberg, M., 197, 266, 412  
Graebe, C., 284  
Greenberg, D. M., 301, 309  
Grignard, M. V., 395  
Grignard reaction, 70, 197, 395  
Grignard reagent, 69, 395  
Grund, Eva, 453  
Guaiacol, 237  
Guanidine, 146  
Guanine, 321, 322, 323  
Gulose, 169  
  
Hæmoglobins, 291, 307  
Hale, William J., 232  
Haller, H. L., 455  
Hannum, Chester, 27  
Hantzsch, A., 439  
Harrington, C. R., 293  
Haworth, W. N., 155, 175  
Heats of combustion, 38  
Helianthine, 273  
Hemiacetal, 154  
Hemimellitene, 194  
Hendess, H., 418  
Heneicosane, 10  
Henriques, V., 299  
Hentriacontane, 10  
Heptamethylene, 36  
Heptane, 10  
Heptyl bromide, 56  
Heptyl chloride, 56  
Heptyl iodide, 56  
Heptylene, 21  
Heptylic acid, 109  
  
Heritage, G., 404  
Hexabiphenylethane, 267  
Hexachloroethane, 60  
Hexacontane, 10  
Hexaethylbenzene, 194  
Hexamethylbenzene, 194  
Hexamethylene, 36  
Hexane, 10  
Hexaphenylethane, 266  
Hexaphenylsilicoethane, 270  
Hexoses, 152, 167  
Hexyl bromide, 56  
Hexyl chloride, 56  
Hexyl iodide, 56  
Hexylene, 21  
Hibbert, H., 398  
Hickinbottom, W. J., 448  
Hinsberg, O., 140  
Hirst, C. T., 400  
Hirst, E. L., 175  
Histidine, 293  
Histones, 307  
Hofmann, A. W., 433, 447  
Hofmann rearrangement, 214, 447  
Hofmeister, F., 299  
Holleman, A. F., 258  
Holmes, E. L., 261  
Homology, 3  
Houben, J., 398  
Hufferd, R. W., 265  
Hunter, Andrew, 301  
Hydrazine, 229  
Hydrazobenzene, 211, 214  
Hydrobenzoin, 446  
Hydrocarbons, acetylene series, 30;  
    alicyclic series, 35; allylene series,  
    29; benzene series, 36, 185; eth-  
    ylene series, 21; methane series, 9  
Hydrolysis, 365; of acetals, 75, 365;  
    of amides, 108, 316; of anhy-  
    drides, 97, 253, 416; of cyanides,  
    247, 369; of esters, 102, 367, 425;  
    of imides, 253, 418; of organo-  
    magnesium compounds, 14, 70,  
    396; of paraffin polyhalides, 243;  
    of proteins, 292, 304  
Hydroquinone, 238  
Hydroxy acids, 111, 131  
Hydroxyacetic acid, 82  
Hydroxyazobenzene, 272  
Hydroxyglutamic acid, 293  
Hydroxylamine, 74  
Hypnone, 245  
Hypoxanthine, 321, 323

- Idose, 169  
Imidazole, 324  
Indanthrene, 285  
Indican, 286  
Indigo, 286, 287  
Indigo white, 287  
Indigoid dyes, 286  
Indoxyl, 286  
Ingold, C. K., 261, 433, 443, 453  
Inulase, 184  
Inulin, 181  
Invertase, 184  
Iodoacetic acid, 82  
Iodobenzene, 205  
Iodoform, 58  
Ionone, 352  
Irone, 353  
Isoamyl bromide, 56  
Isoamyl chloride, 56  
Isoamyl iodide, 56  
Isobutyl alcohol, 45  
Isobutylacetoneitrile, 148  
Isobutylene, 21  
Isocyanates, 149  
Isocyanides, 145  
Isoelectric point, 310  
Isoeugenol, 363  
Isoleucine, 293, 296  
Isomerism, 3, 14, 24, 46, 113  
Isonicotinic acid, 330  
Isoprene, 30  
Isopropyl bromide, 56  
Isopropyl chloride, 56  
Isopropyl iodide, 56  
Isopropylacetoneitrile, 148  
Isopropylethylene, 21  
Isoquinoline, 329
- Jones, L. W., 437  
Jones, W. J., 450
- Karasch, M. S., 27  
Kekulé, August, 187, 190  
Kendall, E. C., 293  
Kenyon, J., 455  
Kerosene, 20  
Kesselkaul, L., 398  
Ketones, 66, 242, 245  
Kidd, H. V., 453  
Killiani, Heinrich, 168  
Kimball, R. H., 425  
King, H., 450  
Kipper, H. B., 232  
Kipping, F. S., 450
- Klarmann, Emil, 301  
Kohler, E. P., 404, 417  
Komppa, G., 361  
Kopp, H., 385  
Kopp's law, 385
- Lachman, Arthur, 245, 445  
Lactase, 184  
Lactic acid, 112 ✓  
Lactose, 178  
Ladenburg, A., 191  
Lævulose, 172  
Lamparter, Walter, 439  
Latimer, W. M., 260  
Lead tetraphenyl, 270  
LeBel, J. A., 115  
Lecithins, 103  
Lecithoproteins, 307  
Leucine, 293, 295, 306  
Levene, P. A., 455  
Lévy, Jeanne, 444  
Lewis, G. N., 288, 457  
Liebermann, C., 284  
Liebig, Justus, 245  
Linalool, 351  
Long, F. A., 451, 458  
Lossen, W., 433  
Lossen rearrangement, 433  
Lycopin, 312  
Lysine, 293, 297  
Lyxose, 165, 167
- Mabery, C. F., 19  
McCoy, H. N., 270  
McKinney, Paul V., 99  
Magenta, 279  
Magnesium pinacolate, 72  
Malachite green, 276  
Maleic acid, 130, 134  
Malonic acid, 121, 123  
Malonic ester, 124, 295, 426  
Maltase, 184  
Maltose, 177  
Mannitol, 49  
Mannose, 169, 173  
Marker, R. E., 455  
Markownikoff, Waldemir, 27  
Martins, C. A., 447  
Marvel, C. S., 447  
Mathews, J. H., 451  
Mayo, Frank R., 27  
Meis, Helmut, 439  
Meisenheimer, Jacob, 210, 439  
Mendelejeff, D., 19

- Menthane, 359  
Menthol, 357  
Menthone, 358  
Mercaptans, 51  
Mesitylene, 194, 195, 219  
Mesitylenic amide, 219  
Mesotartaric acid, 133, 134  
Metaproteins, 307  
Methane, 10, 12  
Methionine, 293  
Methyl alcohol, 42, 46  
Methyl bromide, 56  
Methyl chloride, 11, 56  
Methyl cyanide, 148  
Methyl iodide, 56  
Methyl nitrate, 105  
Methyl nitrite, 105  
Methyl violet, 277  
Methylal, 65  
Methylamine, 143  
Methylaniline, 221, 230  
Methylecgonine, 341  
Methylene chloride, 11, 57, 60  
Methylene iodide, 57  
Methylethyl ether, 63, 64  
Methylethylacetic acid, 82  
Methylethylacetoneitrile, 148  
Methylethylethylene, 21  
Methylglucosides, 156  
Methylisopropyl ether, 64  
Methylphenyl hydrazine, 230  
Methylpropyl ether, 64  
Meyer, Victor, 263  
Michael, Arthur, 442, 448  
Michler's ketone, 223, 277  
Miller, E. J., 175  
Millon's reaction, 308  
Molecular weights, from boiling-point and freezing-point measurements, 463; from osmotic-pressure measurements, 465; from vapor-density measurements, 459  
Monosaccharides, reactions of, 157; configurations of, 163  
Montagne, P. J., 442  
Morphine, 343  
Moser, A., 400  
Mueller, J. H., 293  
Mustard gas, 22  
Mutarotation, 153  
  
Naphthalene, 199  
Naphthalenesulfonic acids, 207, 235  
Naphthols, 235  
Naphtholsulfonic acids, 236  
Naphthylamines, 219  
Naphthylaminesulfonic acids, 220  
Nef, John U., 149  
Nicolet, B. H., 445  
Nicotine, 334  
Nicotinic acid, 330, 332  
Nitriles, 148, 207  
Nitrobenzene, 208, 210, 261  
Nitrobenzoic acids, 248  
Nitroglycerine, 106  
Nitronaphthalene, 200, 210, 220  
Nitrophthalic acid, 200  
Nitrosobenzene, 210, 214  
Nitrosodimethylaniline, 224  
Nitrosophenol, 238  
Nitrotoluene, 209  
Nolte, Otto, 139  
Nonane, 10  
Novocaine, 342  
Noyes, W. A., 44, 265  
Nucleic acid, 305  
Nuclein, 305  
Nucleoproteins, 305, 307  
  
Octamethylene, 36  
Octane, 10  
Octyl bromide, 56  
Octyl chloride, 56  
Octyl iodide, 56  
Octylene, 21  
Ogg, A. R., Jr., 455  
Olefines, 21  
Oleic acid, 93  
Oleopalmitobutyrate, 101  
Ollendorf, Gerhard, 161  
Olson, A. R., 451, 457, 458  
Optical isomerism, 113  
Orekhoff, A., 442  
Orientation, methods of determining, 254  
Orton, K. J. P., 450  
Osborne, T. B., 293, 301  
Ostromisslensky, Iwan, 190  
Oxalic acid, 121  
Oxidation, 370; of alcohols, 41, 90, 243, 371; of aldehydes, 72, 373; of amines, 373; of hydrocarbons, 28, 33, 198, 375; of ketones, 72, 374; of oximes, 378; of phenols, 238, 376; of unsaturated compounds, 29, 376  
Oximes, 74, 244, 437  
Oxyhydroquinone, 240



- Oxyproline, 293, 298
- Palmitic acid, 91, 92, 109
- Paraffin polyhalides, 52, 60
- Paraffin wax, 20
- Paraffins, 9
- Pararosaniline, 278, 280
- Pasteur, L., 114
- Patterson, W. I., 119
- Pauling, L., 457
- Pelc, Joseph, 445
- Pentachloroethane, 60
- Pentamethylbenzene, 194
- Pentamethylene, 36
- Pentane, 10, 16
- Pentoses, 163
- Pepsin, 184
- Peptides, 307
- Peptones, 307
- Perkin, Wm. H., 284, 415
- Perkin reaction, 415
- Petroleum, 19
- pH, 83
- Phenanthraquinone, 203
- Phenanthrene, 201, 203
- Phenol, 208, 233
- Phenolphthalein, 281
- Phenols, dihydric, 236; monohydric, 231; trihydric, 239
- Phenolsulfophthalein, 249
- Phenyl salicylate, 250
- Phenylacetylene, 198
- Phenylalanine, 293, 296, 306
- Phenylbutyric acid, 198
- Phenylchloroamine, 217
- Phenyldibiphenylchloromethane, 266
- Phenylethyl alcohol, 243
- Phenylhydrazine, 75, 229
- Phenylhydroxylamine, 212, 213
- Phillips, Henry, 455
- Phloroglucinol, 240
- Phosgene, 95, 276
- Phosphoproteins, 307
- Phthaleins, 281
- Phthalic acid, 199, 200, 252
- Phthalic anhydride, 253
- Phthalimide, 243, 253
- Phthalyl chloride, 253
- Picolinic acid, 330
- Picramide, 233
- Picric acid, 233
- Picryl chloride, 233
- Pimelic acid, 121
- Pinacol, 72, 441
- Pinacol rearrangement, 441
- Pinacolone, 72, 441
- Pinane, 359
- Pinene, 360
- Piperic acid, 346, 363
- Piperidine, 327, 346
- Piperine, 346, 348
- Piperonal, 346, 363
- Piperonylic acid, 346
- Plimmer, R. H. A., 296
- Polanyi, M., 455
- Polymerization, 30
- Polypeptides, 300, 302
- Polysaccharides, 179
- Porter, C. W., 260, 448, 462
- Prahl, W., 70
- Pratt, L. S., 99
- Prolamins, 307
- Proline, 293, 298, 306
- Propane, 10
- Propargyl alcohol, 51
- Propionic acid, 82, 109
- Propionitrile, 148
- Propyl alcohol, 46
- Propyl bromide, 56
- Propyl chloride, 56
- Propyl iodide, 56
- Propyl nitrate, 105
- Propyl nitrite, 105
- Propylamine, 143
- Propylbenzene, 194
- Propylene, 21
- Propylethylene, 21
- Propylidene chloride, 60
- Protamines, 307
- Proteans, 307
- Proteins, 291; classification of, 306; hydrolysis of, 292, 304; qualitative reactions of, 308; salts of, 309; structure of, 299
- Proteoses, 307
- Pseudocumene, 194
- Ptyalin, 184
- Pulegone, 357
- Pummerer, Rudolf, 270
- Purine, 320
- Purines, 316, 321
- Pyran, 155
- Pyridine, 326
- Pyrimidine, 324
- Pyrimidines, 316, 324
- Pyrocatechol, 236
- Pyrogallol, 239

- Pyrrole, 327  
Pyrroline, 328
- Questions and Problems, 469
- Quinhydrone, 239  
Quinine, 344, 345  
Quinol, 236, 238  
Quinoline, 328  
Quinone, 238, 239  
Quinotoxine, 345
- Racemization, 119  
Racky, G., 270  
Radicals, alkyl, 12; aryl, 192; free, 266  
Ramsperger, H. C., 380  
Raschig, F., 70  
Rather, J. B., 379  
Rayon, 181  
Reduction, 379; of acids, 161, 380; of alcohols, 380; of aldehydes, 72, 162, 379; of azo compounds, 381; of ketones, 72, 162, 246, 379; of nitriles, 147, 381; of nitro compounds, 210, 382  
Reichert-Meissel number, 102  
Reid, E. E., 2, 99, 379  
Reilly, Jos., 448  
Reimer, Marie, 404  
Rennin, 184  
Renning, J., 270  
Resolution of racemic compounds, 117  
Resonance, 385, 388, 394  
Resorcinol, 236, 237  
Reten, 203  
Ribose, 165, 167  
Ritchie, P. D., 118  
Robertson, T. B., 305  
Robinson, R., 261  
Rørdam, H. N. K., 455  
Rosaniline, 278  
Rosenheim, Arthur, 398  
Rosolic acid, 280  
Routala, O., 361  
R-salt, 289  
Ruff, Otto, 161
- Sabatier, P., 379  
Saccharin, 249  
Salicin, 250  
Salicylic acid, 250, 264  
Sallmann, T., 344  
Salol, 250
- Sandmeyer, T., 227  
Schiff's reagent, 76  
Schlenk, W., 270  
Schmidt, C. L. A., 301, 309  
Schroeter, G., 70, 433  
Schulz, Edith, 270  
Scopolamine, 339  
Searle, N. E., 119  
Sebacic acid, 121  
Semiacetal, 154  
Semicarbazide, 76  
Semidine, 214, 215  
Senderens, J. B., 379  
Serine, 293, 296, 306  
Shale, 20  
Sherman, H. C., 315  
Shoppee, C. W., 443  
Sielisch, Johannes, 453  
Simonsen, J. L., 350  
Singer, Ludwig, 398  
Slater, J. C., 457  
Smith, Henry G., 433  
Smith, J. F., 269  
Smith, S. L., 315  
Sorbitol, 49  
Sørensen, S. P. L., 298, 418  
Starch, 180  
Staudinger, H., 245  
Steapsin, 184  
Stearic acid, 92, 109  
Steel, Carolyn, 380  
Steele, B. D., 410  
Steric influences, 254  
Stewart, A. W., 191  
Stewart, Francis B., 99  
Stieglitz, Julius, 433, 435  
Stieglitz rearrangement, 435  
Structure and color, 288  
Strychnine, 342  
Suberic acid, 121  
Succinic acid, 121, 123  
Sucrose, 174  
Sudborough, J. J., 398  
Sulfanilic acid, 231, 273  
Sulfobenzoic anhydride, 249  
Sulfonic acids, 206  
Svedberg, T., 292
- Tartaric acids, 181  
Tautomerism, 239, 423  
Terephthalic acid, 198  
Terpenes, 350  
Terpin, 352, 354  
Terpineol, 354, 356, 360

- Terpinolene, 360  
Tetrachloromethane, 60  
Tetradecane, 10  
Tetramethylammonium chloride, 270  
Tetramethyldiaminobenzophenone, 276, 277  
Tetramethyldiaminotriphenylmethane, 276  
Tetramethylene, 36  
Tetraphenylethylene, 197, 288  
Tetraphenylmethane, 197  
Theobromine, 321, 322  
Theophylline, 321  
Thermochemical relations, 37  
Thiele, J., 191, 387  
Thioindigo, 287  
Thioindigo white, 287  
Thiourea, 146  
Thrombin, 184  
Thurber, Francis, 270  
Thymol, 234, 358  
Thyroxine, 293, 298  
Tiffeneau, M., 442, 444, 445  
T. N. T., 210  
Tollen's reagent, 74  
Toluene, 193, 194  
Toluenesulfonic acid, 249  
Toluic acid, 198, 252, 263  
Toluidine, 218  
Torrey, H. A., 232  
Triaminotriphenylmethane, 275  
Tribromobenzene, 205  
Tribromomesitylene, 205  
Tribromoresorcinol, 237  
Trichloroacetic acid, 82  
Trichlorobenzene, 204  
Trichloropurine, 322, 323  
Tricosane, 10  
Trigonelline, 335  
Trihydric phenols, 239  
Trihydroxybenzene, 239, 240  
Trimethylacetic acid, 82, 109  
Trimethylacetone, 148  
Trimethylbenzoic acid, 264  
Trimethylene, 36  
Trimethylene chloride, 60  
Trimethylethylene, 21  
Trimethylphenylacetic acid, 264  
Trinitrobenzoic acid, 264  
Trinitrophenylmethylnitroamine, 223  
Trinitrotoluene, 209  
Trinitrotriphenyl carbinol, 275  
Triolein, 101  
Tripalmitin, 101  
Triphenylamine, 222  
Triphenylchloromethane, 266  
Triphenylmethane, 196, 268, 275  
Triphenylmethane dyes, 275  
Triphenylmethyl, 266, 268  
Triphenylmethyl peroxide, 266  
Triphenylmethylazobenzene, 197  
Triphenylmethylhydrazobenzene, 197  
Tristearin, 101  
Tropic acid, 336  
Tropidine, 338, 340  
Tropine, 337  
Trypsin, 184  
Tryptophane, 293, 298  
Turley, H. G., 455  
Tuttle, J. R., 397  
Tyrosine, 293, 296  
Undecane, 10  
Urea, 128, 146  
Uric acid, 318, 321  
Valence, 4  
Valeric acid, 82, 109  
Valeronitrile, 148  
Valine, 293, 295, 306  
Vanillin, 363  
Van Slyke, D. D., 309  
Van't Hoff, J. H., 115  
Vaseline, 20  
Vickery, H. B., 293, 301  
Victoria blue, 280  
Vinyl trichloride, 60  
Vitamins, 311  
Vorlander, D., 139  
Wagner, George, 446  
Walden, P., 454  
Walden inversion, 453  
Wallis, E. S., 437  
Warfel, R. R., 44  
Weber, G., 161  
Werner, A., 456  
West, Clarence J., 395  
West, F. L., 270  
Whitmore, Frank, 433  
Wieland, Heinrich, 269, 398, 446  
Wilbur, Paul, 451  
Williamson, R. V., 451  
Wilson, M. M., 45  
Wintergreen, 250, 363

Wislicenus, J., 115  
Witt, O. N., 288  
Witte, Klaus, 210  
Wohler, L., 245  
Worster, F. J., 45  
Wurtz synthesis, 14, 412

Xanthine, 321, 323  
Xanthoproteic test, 308  
Xylenes, 194, 255  
Xylic acids, 263, 265

Xylidines, 218  
Xylitol, 49  
Xylose, 167  
Xylyl bromide, 205

Zanetti, J. E., 201  
Zein, 297  
Zelinsky, N., 397, 400  
Zinc alkyls, 405  
Zymase, 184

